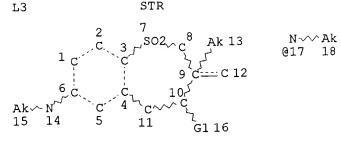
10/699967

(FILE 'REGISTRY' ENTERED AT 09:13:53 ON 26 AUG 2004)

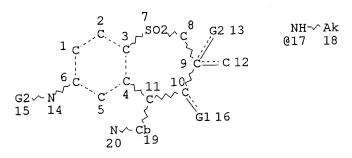


VAR G1=H/OH/NH/17 NODE ATTRIBUTES: DEFAULT MLEVEL IS ATOM DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES: RING(S) ARE ISOLATED OR EMBEDDED NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE

L4 649 SEA FILE=REGISTRY SSS FUL L3
L8 STR



VAR G1=H/OH/NH/17
VAR G2=ME/ET/I-PR/N-PR/I-BU/N-BU/S-BU/T-BU
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS LOC AT 18
GGCAT IS UNS AT 19
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L9 107 SEA FILE=REGISTRY SUB=L4 SSS FUL L8
L12 72 SEA FILE=REGISTRY ABB=ON PLU=ON L9 AND 1/NC

(FILE 'CAPLUS' ENTERED AT 09:29:57 ON 26 AUG 2004) L13 13 S L12

E1 THROUGH E52 ASSIGNED

10/699967

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L13 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:492306 CAPLUS
                            141:17641
DOCUMENT NUMBER:
                           Methods and compositions for the prevention and
TITLE:
                            treatment of Alzheimer's disease with intestinal bile
                            acid reuptake inhibitors
                           Aventis Pharma SA, Fr.
PATENT ASSIGNEE(S):
                            Fr. Demande, 25 pp.
SOURCE:
                            CODEN: FRXXBL
                            Patent
DOCUMENT TYPE:
                            French
LANGUAGE:
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:
                     KIND DATE APPLICATION NO.
     PATENT NO.
                                                 -----
     FR 2848452 A1 20040618 FR 2002-15722 20021212
WO 2004062652 A1 20040729 WO 2003-FR3654 20031210
          W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
              CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
              CO, CR, CU, CZ, DE, DR, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY,
              KG, KZ, MD, RU
          RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
              CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
              NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
              GW, ML, MR, NE, SN, TD, TG
                                                 US 2003-734787
FR 2002-15722
                                                                           20031212
                            A1 20040715
     US 2004138145
                                                                      A 20021212
PRIORITY APPLN. INFO.:
                                                 US 2003-455354P
                                                                      P 20030317
                          MARPAT 141:17641
OTHER SOURCE(S):
     The invention describe the application of the intestinal biliary acid
      reuptake inhibitors for the prevention and the treatment of Alzheimer's
      disease, alone or in conjunction with an HMG-CoA reductase inhibitor , a
      cholesterol uptake inhibitor, a cholesterol synthesis inhibitor or an
      inhibitor of APP secretases.
IT
     252047-40-8
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
      (Biological study); USES (Uses)
         (methods and compns. for prevention and treatment of Alzheimer's
         disease with intestinal bile acid reuptake inhibitors)
      252047-40-8 CAPLUS
RN
      D-Glucitol, 1-[[5-[[3-[(3S,4R,5R)-3-butyl-7-(dimethylamino)-3-ethyl-
CN
      2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-
      5-oxopentyl]amino]-1-deoxy- (9CI) (CA INDEX NAME)
```

Absolute stereochemistry.

REFERENCE COUNT:

11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

2004:60147 CAPLUS

DOCUMENT NUMBER:

140:111291

TITLE:

Preparation of substituted 5-aryl-benzothiepines as ileal bile acid transport and taurocholate uptake

inhibitors

INVENTOR(S):

Lee, Len F.; Banerjee, Shyamal C.; Huang, Horng Chih; Li, Jinglin J.; Miller, Raymond E.; Reitz, David B.;

Tremont, Sanuel J.

PATENT ASSIGNEE(S):

SOURCE:

G.D. Searle and Co., USA

U.S. Pat. Appl. Publ., 235 pp., Cont.-in-part of U.S.

Ser. No. 831,284.

CODEN: USXXCO

DOCUMENT TYPE:

LANGUAGE:

Patent English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004014803 EP 1440972 R: AT, BE, CH, AU 761249 US 2002013476 US 6387924 US 2003171426	A1 A1 DE, DK B2 A1 B2 A1	20030529 20020131 20020514 20030911	US 2002-68297 EP 2004-10088 B, GR, IT, LI, LU, AU 2000-53394 US 2001-828968	20020208 19970311 NL, SE, PT, IE, FI 20000816 20010409
US 6642268 PRIORITY APPLN. INFO.:	В2	20031104	US 1994-305526 US 1995-517051 US 1996-13119P US 1997-816065 US 2001-828968 US 2001-831284	B2 19940913 B1 19950821 P 19960311 A2 19970311 A3 20010409 A2 20010504

AU	1997-23266	A3	19970311
EΡ	1997-915976	A3	19970311
US	1997-40660P	P	19970311
US	1997-831284	B2	19970331
US	1997-68170P	P	19971219
US	1998-109551	A2	19980702
US	1999-275463	A1	19990324
US	1999-443403	A1	19991119
US	2000-676466	A3	20000929

OTHER SOURCE(S):

MARPAT 140:111291

GΙ

$$(R?) q \xrightarrow{\begin{array}{c} (0) n \\ \parallel & R^7 \\ S & \downarrow & R^8 \\ \end{array}}$$

$$R^1 \\ R^2 \\ R^3 \\ R^3$$

The title compds. (I) [wherein q = 1-4; n = 0-2; R1, R2 = H, AΒ (un) substituted (halo) alkyl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy(alkyl), dialkylamino, alkylthio, (polyalkyl)aryl, or cycloalkyl; or R1 and R2 taken together with the atoms to which they are attached = cycloalkyl; R3, R4 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, or SO3R9; R9, R10 = H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), acyl, heterocyclyl, or ammoniumalkyl; or R3 and R4 together = :0, :NOR11, :S, :NNR11R12, :NR9, or :CR11R12; R11, R12 = H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), heterocyclyl, carboxylalkyl, carboalkoxyalkyl, cyanoalkyl, OR9, NR9R10, SR9, S(0)R9, SO2R9, SO3R9, CO2R9, CN, halo, oxo, or CONR9R10; R5, R6 = H, alkyl, aryl, etc.; R7, R8 = H, alkyl; Rx = H, (un)substituted (cyclo)alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl(alkyl), halo(alkyl), (quaternary) heterocyclyl, (quaternary) heteroaryl, polyether, alkoxy, amino, alkylthio, NO2, carboxy, carbamido, etc.] were prepared for the prophylaxis and treatment of hyperlipidemic conditions, such as those associated with atherosclerosis or hypercholesterolemia.

Thus,

KOBu-t was added to a solution of 2-((2-benzy1-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (preparation given) and dry THF

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cooled to -1.6°C to give, after workup, II and III (96% combined yield). The isomers were separated upon recrystn. II inhibited IBAT-mediated

uptake of [14C]-taurocholate in H14 cells with an IC50 of 0.1 μM and reduced serum cholesterol from 143 mg (7%) to 126 mg (2%) compared to control in cholesterol-fed hamsters in a 14-day test. In vitro taurocholate uptake assay data are included for nearly 600 compds. of the invention.

IT 197373-50-5P 197373-51-6P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

RN 197373-50-5 CAPLUS

CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197373-51-6 CAPLUS

CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3, 3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

IT 197373-37-8P 197374-04-2P 197374-59-7P 197375-96-5P 197376-55-9P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

RN 197373-37-8 CAPLUS

CN 1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197374-04-2 CAPLUS

CN 2-Propenamide, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197374-59-7 CAPLUS

CN Propanamide, 3-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197375-96-5 CAPLUS

CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[2-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197376-55-9 CAPLUS

CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[3-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

IT 197373-53-8P 280105-98-8P 647859-06-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

RN 197373-53-8 CAPLUS

CN 1-Pentanaminium, 5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 280105-98-8 CAPLUS

1-Propanesulfonic acid, 3-[[3-[(3R,4S,5S)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 647859-06-1 CAPLUS

1-Pentanaminium, 5-[[3-[(3R,4S,5S)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-N,N,N-triethyl-5-oxo-, rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

L13 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

2003:376848 CAPLUS

DOCUMENT NUMBER:

138:385315

TITLE:

Mono- and di-fluorinated benzothiepines as inhibitors

of apical sodium co-dependent bile acid transport

(ASBT) and taurocholate uptake for treating

hyperlipidemic conditions and methods for preparation

INVENTOR(S):

Koeller, Kevin J.; Tremont, Samuel J.

PATENT ASSIGNEE(S): SOURCE:

G.D. Searle and Co., USA PCT Int. Appl., 589 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

PAT	PATENT NO.					KIND DATE					ICAT:		DATE				
WO.	WO 2003040127						,	WO 2	002-1	JS35:	20021104						
	W:	AE,	AG,	AL,	AM,	AT,	AU,	ΑZ,	ΒA,	BB,	ΒG,	BR,	BY,	ΒZ,	CA,	CH,	CN,
		CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	ES,	FΙ,	GB,	GD,	GE,	GH,
		GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	ΚP,	KR,	ΚZ,	LC,	LK,	LR,
		LS.	LT.	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	ΜZ,	NO,	NΖ,	OM,	PH,
		PL.	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	TM,	TN,	TR,	TT,	TZ,
		UA.	UG.	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW,	AM,	ΑZ,	BY,	KG,	ΚZ,	MD,
			ТJ,		•		•										
	RW:				LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	ŪĠ,	ZM,	ZW,	ΑT,	ΒE,	BG,
	2 (11)	CH.	CY.	CZ.	DE.	DK.	EE,	ES,	FI,	FR,	GB,	GR,	ΙE,	IT,	LU,	MC,	NL,
		PΥ.	SE.	SK.	TR.	BF.	ВJ,	CF.	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,
		•	SN,			,	_ ,	•	•	•	•	•					
119	2004	0678	72	12,	A1 20040408				US 2002-286987					20021104			
					B2 20040525												
0.5 0.5	1//10	546			A1 20040825				EP 2	002-	7787	20021104					
EF	D.	שע	BE	СĦ	DE	DΚ	ES,	FR.	GB.	GR.	TT.	T.T.	LU.	NL.	SE.	MC.	PT,
	R.	AI,	gr,	TT	TAI	ET.	RO,	MK	CY.	AT.	TR.	BG.	CZ.	EE.	sĸ	•	•
DD T O D T MI	ת מוד				цν,	11,	110,	11117	01,	us 2	001-	3308	92P	,	P 2	0011	102
PRIORITI	PRIORITY APPLN. INFO.:							US 2001-330892P WO 2002-US35257									
		/a\ .			MAD												
OTHER SOURCE(S):				MAK	PAI	130:	3033	10									

Mono-fluorinated and di-fluorinated benzothiepine apical Na co-dependent AΒ bile acid transport (ASBT) inhibitors (shown as I; variables defined below; no specific examples are included) are disclosed together with methods of making the same, methods of using the same to treat hyperlipidemic conditions as well as pharmaceutical compns. containing the same compds. For I: X = F, X' = H, F; n = 0-2; m = 0-4; R2A and R2B = Hand hydrocarbyl; R3A, R3B, R5A, and R5B = H, alkyl, cycloalkyl, alkenyl, alkynyl, heterocyclyl, quaternary heterocyclyl, oxo, aryl-R5, -OR9, -NR9R10, -SR9, -S(0)R9, -S02R9, and -S03R9; R9 and R10 = H, hydrocarbyl, amino, and hydrocarbylamino. R5 = H, hydrocarbyl, heterocyclyl, quaternary heterocyclyl, -OR9, -SR9, -S(O)R9, -SO2R9, and -SO3R9; ≥1 R6 radicals = H, halogen, -CN, -NO2, hydrocarbyl, -R5, -OR13, -NR 13R14, -SR13, -S(0)R13, -S(0)2R13, -S03R13, -S+R3R14A-, -NR13OR14, -NR13NR14R15, -OM, -S02OM, -S02NR13R14, -NR14C(0)R13, -C(0)OM, -S(O)NR13R14, -N+R13R14R15A-, -PR13R14, -P(O)R13R4, -P+R13R14R15A-, amino acid residue, peptide residue, polypeptide residue, and carbohydrate

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residue; addnl. details are given in the claims. I (X = X' = F) are claimed to be preparable from the 4-oxo analog and diethylaminosulfur trifluoride; I (X = F; X' = H) are claimed preparable from the 4-hydroxy analog and diethylaminosulfur trifluoride. Hundreds of example prepns. of precursors to I are included, but none of I; most of the example prepns. have appeared in earlier patents (e.g. WO 98/40375). Biol. testing procedures are described but no test results are reported except for the statement that a polyethylene glycol-functionalized benzothiepine (4500 MW; a 4-hydroxy analog of I) inhibited ileal bile acid transport-mediated uptake of 14C-taurocholate in H14 cells.

IT 197373-50-5P 197373-51-6P 197373-52-7P

289037-96-3P 289037-98-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of precursors of mono- and di-fluorinated benzothiepine inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

RN 197373-50-5 CAPLUS

CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197373-51-6 CAPLUS

CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN

197373-52-7 CAPLUS
Pentanamide, 5-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-CNtetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

289037-96-3 CAPLUS RN

Carbamic acid, [3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-CN tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, 3-chloropropyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

571-272-2528 Searcher : Shears

RN 289037-98-5 CAPLUS

CN Urea, N-[3-(chloromethyl)phenyl]-N'-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

IT 280105-90-0P

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of precursors of mono- and di-fluorinated benzothiepine inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

RN 280105-90-0 CAPLUS

Poly(oxy-1,2-ethanediyl), α -[2-[[[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]carbonyl]amino]ethyl]- ω -methoxy-, rel- (9CI) (CA INDEX NAME)

REFERENCE COUNT:

5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

2003:173440 CAPLUS

DOCUMENT NUMBER:

138:215326

TITLE:

Combined preparations, containing 1,4-benzothiepine-

1,1-dioxide derivatives and other active substances

for the treatment of hyperlipidemia

INVENTOR(S):

Glombik, Heiner; Frick, Wendelin; Schaefer,

Hans-Ludwig; Kramer, Werner

PATENT ASSIGNEE(S):

Aventis Pharma Deutschland GmbH, Germany

SOURCE:

PCT Int. Appl., 40 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PAT	PATENT NO.				KIND DATE				APPLICATION NO.						DATE			
WO	wo 2003018024			A1 20030306			WO 2002-EP8908					20020809						
	W:	AE,	AG,	AL,	AM,	AT,	AU,	ΑZ,	BA,	BB,	BG,	BR,	BY,	ΒZ,	CA,	CH,	CN,	
		CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	ES,	FI,	GB,	GD,	GE,	GH,	
		GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	ΚP,	KR,	ΚZ,	LC,	LK,	LR,	
		LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NO,	NZ,	OM,	PH,	
		PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	TM,	TN,	TR,	TT,	TZ,	
		UA,	UG,	UZ,	VN,	YU,	ZA,	ZM,	ZW,	AM,	ΑZ,	BY,	KG,	KZ,	MD,	RU,	TJ,	TM
	RW:	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AT,	BE,	BG,	
		CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	ΙE,	IT,	LU,	MC,	NL,	
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		NE,	SN,	TD,	TG					_					_	0010	200	
	1014				A1			0306								0010		
DE	1014	2456			A1			0320		DE 2	001-	1014	2456		_	0010		
EP	1425	018			A1			0609								0020		
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PRIORIT	Y APP									DE 2 DE 2	001- 001-	1014 1014	0169 2456 08		A 2 A 2	0010 0010 0020	831	

OTHER SOURCE(S):

MARPAT 138:215326

GI

$$R^4$$
 R^5
 R^2
 R^2
 R^3
 R^3
 R^4
 R^3

The invention relates to mixts. of substances, containing 1,4-benzothiepine-1,1-dioxide derivs. of formula (I), in which the functional groups have the indicated meanings, their physiol. acceptable salts and physiol. functional derivs. as well as other active substances for the treatment of metabolic disorders especially hyperlipidemia. The combinations can also include antidiabetics, antiarthrytics etc. A typical capsule contains 100 mg of the drugs and 400 mg triglyceride mixture from coco fatty acids; other formulations are emulsions, tablets, dragees, and solns. Hamster that were fed with cholesterol-rich feed received orally the drug combination once daily for 10 days. Feces was analyzed for bile acids, blood lipid levels were measured and cholesterol was determined from liver.

IT 252047-40-8

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia)

RN 252047-40-8 CAPLUS

CN D-Glucitol, 1-[[5-[[3-[(3S,4R,5R)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

5

ACCESSION NUMBER:

2002:487559 CAPLUS

DOCUMENT NUMBER:

137:63115

TITLE:

Preparation of diphenylazetidinone derivatives as

hypolipidemic agents

INVENTOR(S):

Glombik, Heiner; Kramer, Werner; Flohr, Stefanie; Frick, Wendelin; Heuer, Hubert; Jaehne, Gerhard; Lindenschmidt, Andreas; Schaefer, Hans-Ludwig

PATENT ASSIGNEE(S):

Aventis Pharma Deutschland GmbH, Germany

SOURCE:

PCT Int. Appl., 67 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.				KIND DATE			i	APPLICATION NO.						DATE			
			 Д1	20020627			-	WO 2001-EP14532						20011211			
WO		200	20	ħΤ	λM	יים ע	וומ	AZ,	BA.	BB.	BG.	BR.	BY,	BZ,	CA,	CH,	CN,
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EP	1345	932			A1		2003	0924		EP 2	001-	2713	71			0011	
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10/699967

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IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
                                20040203 BR 2001-16482
                                                                   20011211
                         Α
     BR 2001016482
                                            JP 2002-551564
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     JP 2004516293
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                                20020912
                                            US 2001-21028
    US 2002128252
                         A1
                                20021224
                         B2
    US 6498156
                                                                   20030616
                                            NO 2003-2733
                         A
                                20030814
    NO 2003002733
                                            DE 2000-10064402 A 20001221
DE 2001-10154520 A 20011107
PRIORITY APPLN. INFO .:
                                            WO 2001-EP14532 W 20011211
                       MARPAT 137:63115
OTHER SOURCE(S):
GT
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The compds. are suited for use e.g. as hypolipidemic drugs. The invention discloses preparation of diphenylazetidinone derivs. such as I [R1, R2, R3,

R5, R6 = C0-C30-alkylene-L {optionally containing O, CO, CH:CH, C.tplbond.C, N(alkyl), N(alkylphenyl), NH}, H, F, Cl, Br, I, CF3, NO2, CN, CO2H, CO2(alkyl), CONH2, CONH(alkyl), CON(alkyl)2, alkyl, alkenyl, alkynyl, O-alkyl, SO2NH2, SO2NH(alkyl) SO2N(alkyl)2, S-(alkyl), SO(alkyl), (un)substituted S(CH2)nPh, SO(CH2)nPh, SO2(alkyl), SO2(CH2)nPh, NH2, NH(alkyl), N(alkyl)2, NH(acyl), (un)substituted Ph, O(CH2)nPh; n = 0-6; L = II; R7, R9, R10 = Me, Et, Pr, butyl; R8 = H, OH, NH2, NH(alkyl)], and their physiol. acceptable salts, for their use as hypolipidemic agents. Thus, 1,2-diphenylazetidinone derivative III·trifluoroacetate (IV) was prepared via a multistep synthetic sequence starting from 7-[3-(3-butyl-7-dimethylamino-3-ethyl-4-hydroxy-1,1-dioxo-2,3,4,5-tetrahydro-1H-benzo[b]thiepin-5-yl)-phenylcarbamoyl]-heptanoic acid and 4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxyphenyl]-azetidin-2-one. Azetidinone IV was tested for its cholesterol lowering ability [ED50 = 0.01 mg/mouse].

IT 439113-82-3P 439113-89-0P 439113-91-4P 439113-92-5P 439113-93-6P 439114-23-5P 439114-39-3P 439114-40-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of diphenylazetidinone derivs. as hypolipidemics)

RN 439113-82-3 CAPLUS

Pentanamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-5-[[4-[3-(3-hydroxy-3-phenylpropyl)-2-(4-methoxyphenyl)-4-oxo-1-azetidinyl]phenyl]methyl]amino]-(9CI) (CA INDEX NAME)

PAGE 1-A

OMe
$$\begin{array}{c} \text{OMe} \\ \text{N-Bu} \\ \text{HO-CH-CH}_2\text{-CH}_2\text{-CH}_2 \end{array}$$

PAGE 1-B

-NMe2

439113-89-0 CAPLUS RN

CN fluorophenyl)-3-(3-hydroxy-3-phenylpropyl)-4-oxo-2-azetidinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

$$\begin{array}{c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ &$$

Shears 571-272-2528 Searcher :

RN 439113-91-4 CAPLUS

CN Hexanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[4-[1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

$$\begin{array}{c|c} & & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & &$$

PAGE 1-B

RN 439113-92-5 CAPLUS

CN Hexanediamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N'-[[4-[3-(3-hydroxy-3-phenylpropyl)-2-(4-methoxyphenyl)-4-oxo-1-azetidinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

10/699967

$$\begin{array}{c} \text{Define the problem of the p$$

RN 439113-93-6 CAPLUS

5,8,11-Trioxa-2-azatridecan-13-amide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-1-[4-[1-(4-fluorophenyl)-3-(3-hydroxy-3-phenylpropyl)-4-oxo-2-azetidinyl]phenyl]-3-oxo- (9CI) (CA INDEX NAME)

PAGE 1-A

PAGE 1-B

$$\begin{array}{c|c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 439114-23-5 CAPLUS

CN Octanoic acid, 8-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-8-oxo-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$$

RN 439114-39-3 CAPLUS

CN Acetamide, 2-[2-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-2-oxoethoxy]ethoxy]-N-[[4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxo-1-azetidinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

OME
$$CH_2 - NH - C - CH_2 - CH_2 - CH_2$$

$$CH_2 - CH_2 - CH_2 - CH_2 - CH_2$$

PAGE 1-B

RN 439114-40-6 CAPLUS

5,8,11-Trioxa-2-azatridecan-13-amide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-1-[4-[3-[3-(4-fluorophenyl)-3-hydroxypropyl]-2-(4-methoxyphenyl)-4-oxo-1-azetidinyl]phenyl]-3-oxo- (9CI) (CA INDEX NAME)

PAGE 1-A

OMe
$$CH_2-NH-C-CH_2-O-CH_2-CH_2-$$

$$CH_2-NH-C-CH_2-O-CH_2-CH_2-$$

PAGE 1-B

$$\begin{array}{c|c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$$

IT 439114-09-7 439114-42-8 439114-43-9

RL: RCT (Reactant); RACT (Reactant or reagent) (preparation of diphenylazetidinone derivs. as hypolipidemics)

RN 439114-09-7 CAPLUS

Undecanediamide, N'-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N-methoxy-N-methyl- (9CI) (CA INDEX NAME)

RN 439114-42-8 CAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3-butyl-7-(dimethylamino)-3-ethyl2,3,4,5-tetrahydro-, 1,1-dioxide (9CI) (CA INDEX NAME)

RN 439114-43-9 CAPLUS
CN Pentanamide, 5-bromo-N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]- (9CI) (CA INDEX NAME)

IT 439113-88-9P 439113-94-7P 439113-99-2P

439114-04-2P 439114-14-4P 439114-18-8P 439114-24-6P 439114-27-9P 439114-32-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of diphenylazetidinone derivs. as hypolipidemics)

RN 439113-88-9 CAPLUS

CN Hexanoic acid, 6-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-6-oxo-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 439113-94-7 CAPLUS

CN Acetic acid, [2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-2-oxoethoxy]ethoxy]- (9CI) (CA INDEX NAME)

$$\begin{array}{c} \text{D} \\ \text{D} \\ \text{NMe}_2 \\ \text{HO}_2\text{C}-\text{CH}_2-\text{O}-\text{CH}_2-\text{C}-\text{CH}_2-\text{C}-\text{NH} \\ \\ \text{O} \\ \end{array}$$

RN 439113-99-2 CAPLUS

CN Acetic acid, [2-[2-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-2-oxoethoxy]ethoxy]- (9CI) (CA INDEX NAME)

$$\begin{array}{c} \text{DO} \\ \text{DO} \\ \text{NMe}_2 \\ \text{HO} \\ \text{CC-CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_2\text{-C-NH} \\ \\ \text{OO} \\ \end{array}$$

RN 439114-04-2 CAPLUS
CN Dodecanoic acid, 12-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-12-oxo-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & &$$

RN 439114-14-4 CAPLUS
CN 4,7,10,13,16-Pentaoxanonadecanoic acid, 19-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-19-oxo- (9CI) (CA INDEX NAME)

PAGE 1-A

$${\tt HO_2C-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH$$

PAGE 1-B

$$\begin{array}{c|c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$$

RN 439114-18-8 CAPLUS

CN 4,7,10,13,16,19,22-Heptaoxapentacosanoic acid, 25-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-25-oxo-(9CI) (CA INDEX NAME)

PAGE 1-A

$${\tt HO_2C-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-O-CH_2-CH_2-O-CH_2$$

PAGE 1-B

RN 439114-24-6 CAPLUS

Octanediamide, N'-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N-methoxy-N-methyl-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & \\ & & \\$$

RN 439114-27-9 CAPLUS

CN 2,6,9-Trioxa-3-azaundecan-11-amide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-3-methyl-4-oxo-(9CI) (CA INDEX NAME)

$$\begin{array}{c} \text{MeO} \quad \text{O} \\ \text{MeO} \quad \text{O} \\ \text{Me} - \text{N} - \text{C} - \text{CH}_2 - \text{O} - \text{CH}_2 - \text{C} - \text{CH}_2 - \text{C} - \text{NH} \\ \text{O} \end{array}$$

RN 439114-32-6 CAPLUS

CN Acetic acid, [2-[2-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]ethoxy]ethoxy]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

REFERENCE COUNT:

THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

5

ACCESSION NUMBER:

2001:693092 CAPLUS

DOCUMENT NUMBER:

135:257253

TITLE:

Preparation of tetrahydrobenzothiepines and

naphthalenes useful in combination therapy with HMG Co-A reductase inhibitors for the prophylaxis and treatment of hyperlipidemic conditions and disorders. Keller, Bradley T.; Tremont, Samuel J.; Glenn, Kevin

INVENTOR(S):

C.; Manning, Robert E.

PATENT ASSIGNEE(S):

Pharmacia Corporation, USA

SOURCE:

PCT Int. Appl., 182 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

Searcher :

2

Shears

571-272-2528

10/699967

PATENT INFORMATION:

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KIND DATE
                                      APPLICATION NO.
                                                             DATE
    PATENT NO.
                                        _____
                                                             _____
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                                                             20010308
                      A2
                             20010920
                                       WO 2001-US7505
    WO 2001068096
                       A3 20020725
    WO 2001068096
        W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
            HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
            LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
            SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
            YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
            DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
            BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
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    US 2002061888
                                       US 2002-204672
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    US 2003232834
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                                        US 2003-611942
                                                             20030703
                       A1
                             20040610
                                                         P 20000310
                                        US 2000-188361P
PRIORITY APPLN. INFO.:
                                                         P 20000310
                                        US 2000-188378P
                                                         A3 20010308
                                        US 2001-802279
                                                          B1 20010308
                                        US 2001-802313
                                                         W 20010308
                                        WO 2001-US7505
```

AB A method for the treatment and/or prophylaxis of a hyperlipidemic condition or disorder comprises the administration of ≥1 HMG Co-A reductase inhibitors and one or more specific apical Na codependent bile acid transporter (ASBT) inhibitors is claimed. Thus, (4R,5R)-1-[[4-[4-[3-butyl-3-ethyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxo-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (3,3-di-Bu analog preparation given) 0.375

mg/kg/day and lovastatin 0.45 mg/kg/day orally in dogs reduced serum triglycerides by 37% at 4 wk.

IT 197373-50-5P 197373-51-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of tetrahydrobenzothiepines and naphthalenes useful in combination therapy with HMG Co-A reductase inhibitors for the prophylaxis and treatment of hyperlipidemic conditions and disorders)

RN 197373-50-5 CAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

197373-51-6 CAPLUS RN

1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME) CN

Relative stereochemistry.

L13 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

2001:560070 CAPLUS

DOCUMENT NUMBER:

135:137410

TITLE:

Preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A

reductase inhibitors.

INVENTOR(S):

Keller, Bradley T.; Glenn, Kevin C.; Manning, Robert

PATENT ASSIGNEE(S):

G.D. Searle and Co., USA

SOURCE:

U.S., 356 pp., Cont.-in-part of U.S. Ser. No. 831,284,

abandoned.

CODEN: USXXAM

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.

DATE KIND

APPLICATION NO.

DATE

Searcher :

Shears

571-272-2528

US 6268392	В1	20010731	US 1998-37308		19980309	
EP 1440972	A1	20040728	EP 2004-10088		19970311	
R: AT, BE, CH,		DK, ES, FR,	GB, GR, IT, LI, LU,	NL, SE	E, PT, IE,	FΙ
AU 761249	B2	20030529	AU 2000-53394		20000816	
US 6420417	B1	20020716	US 2000-676466		20000929	
US 2003171426	A1	20030911	US 2002-76091		20020215	
US 6642268	B2	20031104				
US 2004157915	A1	20040812	us 2003-620460		20030717	
PRIORITY APPLN. INFO.:	77.1	200.0012	US 1994-305526	A2	19940912	
PRIORITI APPEN. INFO			US 1995-517051	A1	19950821	
			US 1996-13119P	P	19960311	
			US 1997-40660P	P	19970311	
			US 1997-816065	A2	19970311	
			US 1997-831284		19970331	
			AU 1997-23266		19970311	
			EP 1997-915976		19970311	
			us 1998-37308		19980309	
			US 2000-676466		20000929	
			US 2000-070400 US 2002-76091		20020215	
			05 2002-70091	AI	200202 #0	

OTHER SOURCE(S):

MARPAT 135:137410

Title compds. [I; R = H or 1-4 of alkyl, alkenyl, alkynyl, acyloxy, aryl, aralkyl, halo, etc.; R1, R2 = H, (substituted) alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, alkoxy, dialkylamino, etc.; R1R2C = cycloalkylidene; R3, R4 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, heteroaryl, etc.; R3R4 = O, S, NOR11, etc.; R11 = H, alkyl, alkenyl, alkynyl, aryl, aryl, aryl, aryl, aryl, aryl, aryl, aryl, aryl, heterocyclyl, etc.; R7, R8 = H, alkyl; Z = S00-2], were prepared A composition comprising an ileal bile acid transport inhibitor and an HMG

II

Co-A reductase inhibitor is claimed. Thus, title compound (II) (preparation via 2-mercapto-4-methoxybenzophenone given) at 0.2% as an ileal perfusion in quinea pigs reduced HDL cholesterol from 89 mg% to 76 mg%.

IT 197373-37-8P 197374-04-2P 197374-59-7P 197375-96-5P 197376-55-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

RN 197373-37-8 CAPLUS

CN 1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197374-04-2 CAPLUS

2-Propenamide, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197374-59-7 CAPLUS

Propanamide, 3-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197375-96-5 CAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[2-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197376-55-9 CAPLUS
CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[3-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

IT 197373-50-5P 197373-51-6P 213312-74-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

RN 197373-50-5 CAPLUS

CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197373-51-6 CAPLUS

CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 213312-74-4 CAPLUS

CN Pentanamide, 5-chloro-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

REFERENCE COUNT:

THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

76

ACCESSION NUMBER:

2000:590035 CAPLUS

DOCUMENT NUMBER:

133:193089

TITLE:

Preparation of substituted 5-aryl-benzothiepines as ileal bile acid transport and taurocholate uptake

inhibitors

INVENTOR(S):

Lee, Len F.; Banerjee, Shyamal C.; Huang, Horng-chih; Li, Jinglin J.; Miller, Raymond E.; Reitz, David B.;

Tremont, Samuel J.

PATENT ASSIGNEE(S):

G.D. Searle and Co., USA

SOURCE:

U.S., 191 pp., Cont.-in-part of U.S. Ser. No.

109,551.

CODEN: USXXAM

DOCUMENT TYPE:

Patent English

LANGUAGE: Er FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

PATENT NO.					KIND DATE					ICAT	ION I		DATE				
	6107494			Α		2000	0822		US 1	999-	2754	63		1	9990	324	
	1440972			A1		2004	0728		EP 2	004-	1008	8		1	9970	311	
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	MX.	NO.	NZ,	PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	TM,	TR,	
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	ТJ.	TM															
	RW: GH,	GM,	KE,	LS,	MW,	SD,	SL,	SZ,	UG,	ZW,	AT,	BE,	CH,	CY,	DE,	DK,	
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	1091953			A1		2001	0418		EP 1	999-	9317	69		1	9990	629	
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JР	20025194	18		Т2		つんへつ	ハフハつ		י סד.	$\alpha\alpha\alpha$	5580	u i			9990	n/9	
	509621			Α		2002	0829		IV Zi	999-	いいっし	2.1		1	9990	629	
	256122			E		2003	1215		AT 1	999-	9317						
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US	6387924 20021881	19		A1		2002	1212		US 2	002-	7260	0		2			
	20031714					2003	0911		US 2	002-	7609	1		2	0020	215	
	6642268			В2			1104										
	20042038	91		A2		2004	0722		JP 2	004-	5047	3		_	0040		
UF	Y APPLN.		. :						US 1	994-	3055	26			9940		
									US 1	.995-	5170	51			9950		
									US 1	996-	1311	Q P		n 1	9960	211	
												J		_			
										997-				B2 1	9970	311	
									US 1		8160	65		B2 1 B2 1	9970 9970	311 331	
									US 1 US 1	997-	8160 8312	65 84		B2 1 B2 1 P 1	9970	311 331 219	

AU	1997-23266	A3	19970311
ΕP	1997-915976	A3	19970311
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ΕP	1998-962044	A3	19981216
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JP	2000-558091	A 3	19990629
WO	1999-US12828	W	19990629
US	1999-443403	A 1	19991119
US	2000-676466	A3	20000929
US	2000-581897	A3	20001002

OTHER SOURCE(S):

MARPAT 133:193089

$$(R?) q \xrightarrow{(O)_{R}} R7$$

$$R8$$

$$R1$$

$$R2$$

$$R6$$

$$R5$$

$$R4$$

The title compds. (I) [wherein q = 1-4; n = 2; R1 and R2 = independently H AB or (un) substituted (halo) alkyl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy(alkyl), dialkylamino, alkylthio, (polyalkyl)aryl, or cycloalkyl; or R1 and R2 taken together with the atoms to which they are attached = cycloalkyl; R3 and R4 = independently H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, OR9, NR9R10, SR9, S(0)R9, SO2R9, or SO3R9; R9 and R10 = independently H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), acyl, heterocyclyl, or ammoniumalkyl; or R3 and R4 together = :0, :NOR11, :S, :NNR11R12, :NR9, or :CR11R12; R11 and R12 = independently H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), heterocyclyl, carboxylalkyl, carboalkoxyalkyl, cyanoalkyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, SO3R9, CO2R9, CN, halo, oxo, or CONR9R10; R5 = substituted aryl; R6 = H; R7 and R8 = independently H or alkyl; Rx = independently H or (un) substituted (cyclo)alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl(alkyl), halo(alkyl), (quaternary) heterocyclyl, (quaternary) heteroaryl, polyether, alkoxy, amino, alkylthio, NO2, carboxy, carbamido, etc.] where prepared for the prophylaxis and treatment of hyperlipidemic conditions, such as those associated with atherosclerosis or hypercholesterolemia.

Ι

Thus,

KOBu-t was added to a solution of $2-((2-benzy1-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (preparation given) and dry THF cooled to <math>-1.6\,^{\circ}$ C to give, after workup, II and III (96% combined yield). The isomers were separated upon recrystn. II inhibited

IBAT-mediated

uptake of [14C]-taurocholate in H14 cells with an IC50 of 0.1 μM and reduced serum cholesterol from 143 mg (7%) to 126 mg (2%) compared to control in cholesterol-fed hamsters in a 14-day test. In vitro taurocholate uptake assay data are included for nearly 600 compds. of the invention.

IT 197373-50-5P 197373-51-6P 289037-96-3P 289037-98-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

RN 197373-50-5 CAPLUS

CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197373-51-6 CAPLUS

CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 289037-96-3 CAPLUS

CN Carbamic acid, [3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, 3-chloropropyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 289037-98-5 CAPLUS

Urea, N-[3-(chloromethyl)phenyl]-N'-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

IT 197373-37-8P 197374-04-2P 197374-59-7P 197375-96-5P 197376-55-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and taurocholate uptake inhibitors)

RN 197373-37-8 CAPLUS

CN 1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197374-04-2 CAPLUS

CN 2-Propenamide, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN

197374-59-7 CAPLUS
Propanamide, 3-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-CN tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

197375-96-5 CAPLUS RN

1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[2-CN (dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

571-272-2528 Shears Searcher :

RN 197376-55-9 CAPLUS

CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[3-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

REFERENCE COUNT:

THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

2000:456922 CAPLUS

DOCUMENT NUMBER:

133:94515

TITLE:

Combinations for cardiovascular indications

INVENTOR(S):

Keller, Bradley T.; Reitz, David B.; Schuh, Joseph R.; Sikorski, James A.; Tremont, Samuel J.; Lappe, Rodney

W.

PATENT ASSIGNEE(S):

G.D. Searle and Co., USA

SOURCE:

PCT Int. Appl., 248 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent English

LANGUAGE:

. 0

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

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A1 20000706 WO 1999-US27946
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              CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
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                                                                                  19991217
                                                    NZ 1999-512532
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     NZ 512532
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     PT 1140187 T 20040130
ZA 2001005056 A 20020620
ZA 2001005059 A 20020620
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ZA 2001005060 A 20020920
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US 2004058908 A1 20040325
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US 2004048846 A1 20040311
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PRIORITY APPLN. INFO .:
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P 19990707
US 1999-142603P
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                   P 19990713
US 1999-143550P
                   A3 19991217
EP 1999-965035
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EP 1999-965902
                   A3 19991217
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                   A3 19991217
EP 1999-967140
                   A3 19991217
US 1999-465642
                   A3 19991217
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                   B1 19991217
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us 1999-466470
                   A3 19991217
US 1999-466592
                   A3 19991217
                   B3 19991217
US 1999-466596
WO 1999-US27946
                   W 19991217
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The present invention provides combinations of cardiovascular therapeutic AΒ compds. for the prophylaxis or treatment of cardiovascular disease including hypercholesterolemia and atherosclerosis. Combinations disclosed include an ileal bile acid transport inhibitor combined with a cholesteryl ester transport protein (CETP) inhibitor, a fibric acid derivative, a nicotinic acid derivative, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist, a phytosterol, a stanol, an antihypertensive agent, or others. Further combinations include a CETP inhibitor with a fibric acid derivative, a nicotinic acid derivative, a bile acid sequestrant, a microsomal triglyceride transfer protein inhibitor, a cholesterol absorption antagonist, or others.

197373-37-8D, enantiomers 280105-90-0D, enantiomers IT280105-98-8D, enantiomers

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combinations for cardiovascular agents for treatment of cardiovascular indications)

197373-37-8 CAPLUS RN

1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-CN 2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

280105-90-0 CAPLUS RN

Poly(oxy-1,2-ethanediyl), α -[2-[[[[3-[(4R,5R)-3,3-dibutyl-7-CN (dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5yl]phenyl]amino]carbonyl]amino]ethyl]-w-methoxy-, rel- (9CI) (CA INDEX NAME)

280105-98-8 CAPLUS RN

1-Propanesulfonic acid, 3-[[3-[(3R,4S,5S)-3-butyl-7-(dimethylamino)-3-CN ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

2

ACCESSION NUMBER:

1999:795803 CAPLUS

DOCUMENT NUMBER:

132:35625

TITLE:

Amino acid containing benzo[b] thiepine 1,1-dioxide

derivatives as hypolipemic agents

INVENTOR(S):

Frick, Wendelin; Enhsen, Alfons; Glombik, Heiner;

Heuer, Hubert

PATENT ASSIGNEE(S):

Hoechst Marion Roussel Deutschland G.m.b.H., Germany

SOURCE:

PCT Int. Appl., 28 pp. CODEN: PIXXD2

Patent

DOCUMENT TYPE: LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.					KIN		DATE			APPL:		ION 1	DATE					
WO 9964410						1999	1216	1					19990528					
	W:	AE,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CU,	CZ,	
		DE.	DK.	EE,	ES,	FI,	GB,	GD,	GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	
		JP.	KE,	KG,	KP,	KR,	ΚZ,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	MD,	MG,	MK,	
		MN.	MW,	MX,	NO,	NZ,	PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	
		TM,	TR,	TT,	UA,	UG,	US,	UZ,	VN,	YU,	ZA,	ZW,	AM,	ΑZ,	BY,	KG,	KΖ,	
		MD,	RU,	ТJ,	TM													
	RW:	GH,	GM,	ΚE,	LS,	MW,	SD,	SL,	SZ,	UG,	ZW,	AT,	ΒE,	CH,	CY,	DE,	DK,	
		ES,	FI,	FR,	GB,	GR,	IE,	IT,	LU,	MC,	NL,	PT,	SE,	BF,	ВJ,	CF,	CG,	
		CI,	CM,	GΑ,	GN,	GW,	ML,	MR,	NE,	SN,	TD,	TG			-		610	
DE	1982	5804			A1		1999	1216		DE 1	998-	1982	5804		1	9980	PT0	
DΕ	1982	5804			C2		2000	0824		_					-	0000		
CA	2334								CA 1999-2334775						19990528			
ΑU	9945	019			A1				AU 1999-45019							9990	528	
AU	7532						2002	-							_			
ΕP	1086	092			A1		2001	0328		EP 1	999-	9277	84		1	9990.	528	
ΕP	1086	092			В1		2002	1113								_		
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	IT,	LI,	LU,	NL,	SE,	PT,	IE,	FΊ
BR	9912							0410		BR 1	999-	1218	8		1	9990	528	

TR 200003634	T 2	20010621	ΤR	2000-200003634		19990528
JP 2002517491	T 2	20020618	JP	2000-553419		19990528
AT 227715	E	20021115	ΑT	1999-927784		19990528
ES 2182535	Т3	20030301	ES	1999-927784		19990528
PT 1086092	${f T}$	20030331	PT	1999-927784		19990528
RU 2215001	C2	20031027	RU	2001-101491		19990528
TR 200003632	T2	20010420	TR	2000-200003632		19990529
AU 761249	B2	20030529	AU	2000-53394		20000816
ZA 2000007060	A	20010718	zA	2000-7060		20001130
ZA 2000007061	A	20010718	zA	2000-7061		20001130
US 6387944	B1	20020514	US	2000-719047		20001207
US 2002045583	A1	20020418	US	2001-773772		20010202
US 6441022	B2	20020827				
PRIORITY APPLN. INFO.:			DE	1998-19825804	Α	19980610
			AU	1997-23266	АЗ	19970311
			WO	1999-EP3701	W	19990528
			US	1999-398315	A1	19990920
OTHER SOURCE(S):	MARPAT	132:35625				

GI

AB Title compds. such as I (mixture of diastereoisomers) were prepared as hypolipemic agents. Thus, I was prepared in 2 sequences from racemic II and Fmoc-D-lys(Boc)-OH, followed by removal of the Fmoc group with Et2NH. I was ≥20 times more active than 3 analogous comparison substances in tests of fecal separation of 14C-taurocholic acid in rats.

IT 252372-02-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as hypolipemic

agents)

RN 252372-02-4 CAPLUS

CN D-Lysinamide, N6-[(1,1-dimethylethoxy)carbonyl]-D-lysyl-N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-N6-[(1,1-dimethylethoxy)carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

^{*} STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

IT 252047-42-0

agents)

RN 252047-42-0 CAPLUS

CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-, 1,1-dioxide, (3R,4S,5S)-rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

IT 252372-00-2P 252372-01-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as hypolipemic

agents)

RN 252372-00-2 CAPLUS

CN Carbamic acid, [(1R)-1-[[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]carbonyl]-5-[[(1,1-dimethylethoxy)carbonyl]amino]pentyl]-,9H-fluoren-9-ylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 252372-01-3 CAPLUS

CN Carbamic acid, [(5R)-5-amino-6-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-6-oxohexyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Et
$$n-Bu$$
 NMe_2 NH_2 HN R (CH_2) A NH_2 $OBu-t$

REFERENCE COUNT:

THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

1

ACCESSION NUMBER: 1999:795802 CAPLUS

DOCUMENT NUMBER: 132:22884

TITLE: Preparation of benzothiepine-1,1-dioxides as

hypolipemics

INVENTOR(S): Frick, Wendelin; Enhsen, Alfons; Glombik, Heiner;

Heuer, Hubert

PATENT ASSIGNEE(S): Hoechst Marion Roussel Deutschland G.m.b.H., Germany

SOURCE: PCT Int. Appl., 30 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

WO 9964409 A2 19991216 WO 1999-EP3743 1999 WO 9964409 A3 20000302 W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MC	, CZ,
DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG	, CZ,
DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG	
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MO	. IS.
	, MK.
MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SI	. T.T.
TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KO	, 10, K7
MD, RU, TJ, TM	, 12,
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE	שת
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF	, DK,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG	, CG,
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TD 20000524 TD 20010624 TD 2000 20000524	
12 20010621 TR 2000-200003634 1999	0528
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CA 2334773 AA 19991216 CA 1999-2334773 1999	0529
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AU 752633 B2 20020926 EP 1086113 A2 20010328 EP 1999-927802 1999 EP 1086113 B1 20040211	0529
EP 1086113 B1 20040211	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT	IE, FI
TR 200003632 T2 20010420 TR 2000-200003632 1999	
JP 2002517490 T2 20020618 JP 2000-553418 1999 JP 3374129 B2 20030204 NZ 508681 A 20020628 NZ 1999-508681 1999)529
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RU 2220141 C2 20031227 RU 2001-101499 1999)529
AT 259372 E 20040215 AT 1999-927802 1999 US 6221897 B1 20010424 US 1999-398315 1999 AU 761249 B2 20030529 AU 2000-53394 2000 ZA 2000007060 A 20010718 ZA 2000-7060 2000 ZA 2000007061 A 20010718 ZA 2000-7061 2000)529
US 6221897 B1 20010424 US 1999-398315 1999	920
AU 761249 B2 20030529 AU 2000-53394 2000	816
ZA 2000007060 A 20010718 ZA 2000-7060 2000	.130
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NO 2000006251 A 20010207 NO 2000-6251 2000	.208
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PRIORITY APPLN. INFO.: DE 1998-19825804 A 1998	
US 1996-13119P P 1996	
AU 1997-23266 A3 1997	
WO 1999-EP3743 W 1999	
US 1999-398315 A1 1999	
US 2001-773772 A1 2001	
US 2002-201050 A1 2002	
OTHER SOURCE(S): MARPAT 132:22884	, 4 4
GI	

AB Title compds. [I; R = C6H4NHZR3; R1,R4,R5 = Me, Et, Pr, Bu; R2 = H, OH, amino(alkyl); R3 = sugar residue; Z = bond, carbonyl(alkylene), CONH, etc.] were prepared Thus, I [R = C6H4(NHR')-3, R1 = Et, R2 = OH, R4 = R5 = Me](II; R' = H) was amidated by penta-O-acetyl-D-gluconic acid and the product deprotected to give II (R' = gluconoyl) as a mixture of diastereomers. Data for biol. activity of I were given.

IT 252047-36-2P 252047-37-3P 252047-38-4P 252047-39-5P 252047-40-8P 252047-41-9P 252208-66-5P 252208-67-6P 252208-68-7P 252208-69-8P 252208-70-1P 252208-71-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of benzothiepine-1,1-dioxides as hypolipemics)

252047-36-2 CAPLUS

CN D-Glucitol, 1-[[5-[[3-[(3R,4S,5S)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN

RN 252047-37-3 CAPLUS

CN D-Glucitol, 1-deoxy-1-[[5-[[3-[(4S,5S)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 252047-38-4 CAPLUS

CN D-Gluconamide, N-[3-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, 2,3,4,5,6-pentaacetate (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 252047-39-5 CAPLUS

CN D-Gluconamide, N-[3-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 252047-40-8 CAPLUS

CN D-Glucitol, 1-[[5-[[3-[(3S,4R,5R)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 252047-41-9 CAPLUS

CN D-Glucitol, 1-deoxy-1-[[5-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$n-Bu$$
 $n-Bu$
 $n-Bu$

RN 252208-66-5 CAPLUS

CN D-Gluconamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 252208-67-6 CAPLUS

CN D-Gluconamide, N-[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, 2,3,4,5,6-pentaacetate (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 252208-68-7 CAPLUS

CN D-Gluconamide, N-[11-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-11-oxoundecyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 252208-69-8 CAPLUS

CN D-Gluconamide, N-[5-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]-, 2,3,4,5,6-pentaacetate (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 252208-70-1 CAPLUS

CN D-Gluconamide, N-[5-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$\begin{array}{c} \text{Et} \\ \text{n-Bu} \\ \text{HO} \\ \\ \text{HN} \\ \text{O} \\ \\ \text{O} \\ \\ \text{OH} \\ \text{OH} \\ \text{OH} \\ \\$$

RN 252208-71-2 CAPLUS

CN D-Glucitol, 1-{acetyl[5-[[3-[3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-5-oxopentyl]amino]-1-deoxy-, 2,3,4,5,6-pentaacetate (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 252047-42-0 252047-43-1

RL: RCT (Reactant); RACT (Reactant or reagent) (preparation of benzothiepine-1,1-dioxides as hypolipemics)

RN 252047-42-0 CAPLUS

CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-, 1,1-dioxide, (3R,4S,5S)-rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 252047-43-1 CAPLUS

Pentanamide, 5-bromo-N-[3-[(3R,4S,5S)-3-butyl-7-(dimethylamino)-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

L13 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

1998:621210 CAPLUS

DOCUMENT NUMBER:

129:260353

TITLE:

Preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A

reductase inhibitors.

INVENTOR(S):

Reitz, David B.; Lee, Len F.; Li, Jinglin J.; Huang, Horng-Chih; Tremont, Samuel J.; Miller, Raymond E.; Baneriee, Shyamal C.; Manning, Robert E.; Glenn, Kevin

C.; Keller, Bradley T.

PATENT ASSIGNEE(S):

G.D. Searle and Co., USA; et al.

SOURCE:

PCT Int. Appl., 477 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.					KIND		DATE			APPL:	ICAT:	DATE					
,,,						19980917 19981203		,	WO 1:			19980310					
WO	W:	AL, DK,	AM, EE,	AT, ES,	AU, FI,	AZ, GB,	BA, GE, LR,	BB, GH,	GM,	GW,	HU,	ID,	IL,	IS,	JP,	ΚE,	KG,
	DM.	NO, UA,	NZ, UG,	PL, US,	PT, UZ,	RO, VN,	RU, YU, SD,	SD, ZW,	SE, AM,	SG, AZ,	SI, BY,	SK, KG,	SL, KZ,	TJ, MD,	TM, RU,	TR, TJ,	TT, TM
	KW:	FR,	GB, GN,	GR, ML,	IE, MR,	IT, NE,	LU, SN,	MC, TD,	NL, TG	PT,	SE,	BF,	ВJ,	CF,	CG,	CI,	CM,
	AU 9864408 AU 730024							AU 1998-64408						19980310			
	P 971744			A2		2000	0119		EP 1998-910075 GB, GR, IT, LI, LU, N								
ΝZ	R:	IE,	FI				2001							1411,		9980	

BR 9808013 JP 2002500628 NO 9904390 AU 761249 US 2003171426	A T2 A B2 A1	20010925 20020108 19991104 20030529 20030911	JP NO AU	1998-8013 1998-539594 1999-4390 2000-53394 2002-76091		19980310 19980310 19990910 20000816 20020215
US 6642268 PRIORITY APPLN. INFO.:	B2	20031104	US US US US AU	1997-40660P 1994-305526 1995-517051 1996-13119P 1997-23266 1997-816065	B1 P A3	19970311 19940913 19950821 19960311 19970311
			WO	1997-831284 1998-US3792 2000-676466	B3 W A3	19970331 19980310 20000929

OTHER SOURCE(S):

MARPAT 129:260353

GΙ

Co-A

$$(R^9)_{q} \xrightarrow[R6]{R^7} R^8$$

$$R^1$$

$$R^2$$

$$R^3$$

$$R^3$$

$$R^4$$

$$R^3$$

$$R^4$$

$$R^3$$

$$R^4$$

$$R^3$$

$$R^4$$

$$R^3$$

$$R^4$$

$$R^3$$

$$R^4$$

$$R^4$$

$$R^3$$

$$R^4$$

$$R$$

AB Title compds. [I; q = 1-4; n = 0-2; R1, R2 = H, (substituted) alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, alkoxy, dialkylamino, etc.; R1R2C = cycloalkylidene; R3, R4 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, heteroaryl, etc.; R3R4 = 0, S, NOR11, etc.; R11 = H, alkyl, alkenyl, alkynyl, aryl, aralkyl, etc.; R5, R6 = H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, etc.; R7, R8 = H, alkyl; R9 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, aralkyl, halo, etc.], were prepared A composition comprising an ileal bile acid transport inhibitor and an HMG

reductase inhibitor is claimed. Thus, title compound (II) (preparation via 2-mercapto-4-methoxybenzophenone given) at 0.2% as an ileal perfusion in guinea pigs reduced HDL cholesterol from 89 mg% to 76 mg%.

IT 197373-37-8P 197374-04-2P 197374-59-7P 197375-96-5P 197376-55-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

RN 197373-37-8 CAPLUS

CN 1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197374-04-2 CAPLUS
CN 2-Propenamide, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197374-59-7 CAPLUS
CN Propanamide, 3-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5tetrahydro-4-bydroxy-1,1-dioxide-1-benzethiepin-5-yllphenyll-, rel- (9CI)

tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197375-96-5 CAPLUS

CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[2-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197376-55-9 CAPLUS

CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[3-(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

IT 197373-50-5P 197373-51-6P 213312-74-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

RN 197373-50-5 CAPLUS

CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197373-51-6 CAPLUS

CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 213312-74-4 CAPLUS

CN Pentanamide, 5-chloro-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

L13 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

1997:623163 CAPLUS

DOCUMENT NUMBER:

127:307312

TITLE:

Novel benzothiepines having activity as inhibitors of ileal bile acid transport and taurocholate uptake

INVENTOR(S):

Reitz, David B.; Lee, Len F.; Li, Jinglin J.; Huang, Horng-Chih; Tremont, Samuel J.; Miller, Raymond E.;

Banerjee, Shyamal C.

PATENT ASSIGNEE(S):

G.D. Searle and Co., USA; Reitz, David B.; Lee, Len F.; Li, Jinglin J.; Huang, Horng-Chih; Tremont, Samuel

J.; Miller, Raymond E.; Banerjee, Shyamal C.

SOURCE:

PCT Int. Appl., 406 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

PATENT	KIND DATE				APPL	ICAT:	ION :		DATE								
WO 973	3882			A1		1997	0918	,	wo 1	997-1	US40	76		1	9970	311	
W:	AT.	AM.	AT.	AU.	AZ.	BA,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CU,	CZ,	DΕ,	
	DK.	EE,	ES.	FI.	GB,	GE,	HU,	IL,	IS,	JP,	ΚE,	KG,	KΡ,	KR,	KZ,	LC,	
	T.K.	LR.	LS.	LT.	LU,	LV,	MD,	MG,	MK,	MN,	MW,	MΧ,	NO,	ΝZ,	PL,	PT,	
	RO,	RU,	SD,	SE,	SG,	si,	SK,	ТJ,	TM,	TR,	TT,	UA,	UG,	US,	UΖ,	VN,	
	AM.	AZ.	BY,	KG,	KZ,	MD,	RU,	ТJ,	TM								
RW	: GH.	KE.	LS,	MW.	SD,	SZ,	ŬĠ,	AT,	BE,	CH,	DE,	DK,	ES,	FI,	FR,	GB,	
•	GR.	IE.	IT,	LU,	MC,	NL,	PT,	SE,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	
		MD	NE	SM	- מידי	TG											
CA 224				ΑA	•	1997 1997	0918		CA 1	997-	2248	586		1	9970	311	
972 וזב	3266			A1		1997	1001	,	AU 1	997-	2326	6		1	9970	311	
723 זומ	123			B2		2000	0817										
EP 888	333			A1		1999	0107		EP 1	997-	9159	76		1	9970	311	
R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	IT,	LI,	LU,	ИL,	SE,	PT,	ΙE,	FI
CM 122	1414			Δ		1999	0630		CN 1	997-	1945	03		1	9970	311	
CN 111 BR 970 JP 200	0494			В		2003	0604										
BR 970	8042			A		1999	0727		BR 1	997-	8042			1	9970	311	
JP 200	15266	27		Т2		2001	1218		JP 1	997-	5328	75		1	9970	311	
RU 220	2549			C2		2003	0420		RU 1	998-	1186	43		1	9970	3 I I	
EP 144	0972			A1		2004	0728		EP 2	004-	1008	8			9970		
R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	IT,	LI,	LU,	ΝL,	SE,	PT,	IE,	FΙ
NO 980	4146			Α		1998	1030		NO 1	998-	4146			1	9980	909	
R: NO 980 AU 761 US 200 US 664	249			В2		2003	0529		AU 2	000-	5339	4		2	0000	816	
US 200	31714	26		A1		2003	0911		US 2	002-	7609	1		2	0020	215	
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									US 1	997-	8160	65		A 1	9970	311	
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															9970		
									WO 1	997-	US40	76		W 1	9970	311	
									US 1	997-	8312	84		B3 1	9970	331	
									US 2	000-	6764	66		A3 2	0000	929	
HER SOURC	E(S):			MAR	PAT	127:	3073	12									

Novel benzothiepines I [q = 1-4; n = 0-2; R = H, halo, (un) substitutedAΒ alk(en/yn)yl, acyloxy, aryl, heterocyclyl, OH or NH2 or SH or derivs., etc.; R1, R2 = H, (un) substituted and/or heteroatom-replaced alk(en/yn)yl, cycloalkyl, aryl, alkoxy, alkylthio, dialkylamino; or CR1R2 = C3-10 cycloalkylidene; R3, R4 = H, alk(en/yn)yl, acyloxy, aryl, heterocyclyl, OH or NH2 or SH or derivs.; or R3R4 = O, S, NH, NOH, NNH2, CH2 or derivs.; R5, R6 = H, (un) substituted alk(en/yn) yl, cycloalkyl, aryl, heterocyclyl, OH or SH or derivs.; R7, R8 = H, alkyl] and their derivs. and analogs are provided. Also provided are pharmaceutical compns. containing I and methods of their medical use, particularly in the prophylaxis and treatment of hyperlipidemic conditions, such as those associated with atherosclerosis or hypercholesterolemia. For instance, the keto aldehyde II was cyclized by Zn/TiCl3, and the resultant cycloolefin was oxidized and epoxidized by m-ClC6H4C(O)OOH and hydrogenated over Pd/C to give epimeric title compds. $\alpha-$ and $\beta-$ III in 25% and 13% yield, plus addnl. compds. In a test for inhibition of IBAT-mediated uptake of [14C]-taurocholate in H14 cells in vitro, β -III had an IC50 of 5 μM .

IT 197373-50-5P 197373-51-6P 197373-52-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of benzothiepines as antihyperlipidemics)

RN 197373-50-5 CAPLUS

CN 1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197373-51-6 CAPLUS
CN 1-Benzothiepin-4-ol, 5-(3-aminophenyl)-3,3-dibutyl-7-(dimethylamino)2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 197373-52-7 CAPLUS
CN Pentanamide, 5-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

197373-37-8P 197374-04-2P 197374-59-7P ΙT 197375-96-5P 197376-55-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of benzothiepines as antihyperlipidemics)

197373-37-8 CAPLUS RN

1-Propanesulfonic acid, 3-[[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-CN2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]amino]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

197374-04-2 CAPLUS RN

2-Propenamide, N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-CN tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

571-272-2528 Shears Searcher :

197374-59-7 CAPLUS RN

Propanamide, 3-bromo-N-[3-[(4R,5R)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-CN tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

197375-96-5 CAPLUS RN

1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[2-CN(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

571-272-2528 Shears Searcher :

197376-55-9 CAPLUS RN

1-Benzothiepin-4-ol, 3,3-dibutyl-7-(dimethylamino)-5-[3-CN

(dimethylamino)phenyl]-2,3,4,5-tetrahydro-, 1,1-dioxide, (4R,5R)-rel-

(9CI) (CA INDEX NAME)

Relative stereochemistry.

FILE 'CAOLD' ENTERED AT 09:31:14 ON 26 AUG 2004 0 S L12

(FILE 'USPATFULL' ENTERED AT 09:31:19 ON 26 AUG 2004) 12 S L12 L15

L15 ANSWER 1 OF 12 USPATFULL on STN

ACCESSION NUMBER:

2004:204023 USPATFULL

TITLE:

L14

Combination therapy employing ileal bile acid transport

inhibiting benzothiepines and HMG Co-A reductase

inhibitors

INVENTOR(S):

Keller, Bradley T., Chesterfield, MO, UNITED STATES Glenn, Kevin C., Maryland Heights, MO, UNITED STATES

Manning, Robert E., St. Louis, MO, UNITED STATES

PATENT ASSIGNEE(S):

G.D. Searle & Co., Chicago, IL, UNITED STATES, 60680

(U.S. corporation)

DATE KIND NUMBER 20040812 Α1 US 2004157915 PATENT INFORMATION:

Searcher :

Shears

571-272-2528

APPLICATION INFO.:

20030717 (10) US 2003-620460 A1

Continuation of Ser. No. US 2002-76091, filed on 15 Feb RELATED APPLN. INFO.: 2002, GRANTED, Pat. No. US 6642268 Division of Ser. No. US 2000-676466, filed on 29 Sep 2000, GRANTED, Pat. No. US 6420417 Division of Ser. No. US 1998-37308, filed on

9 Mar 1998, GRANTED, Pat. No. US 6268392

Continuation-in-part of Ser. No. US 1997-831284, filed on 31 Mar 1997, ABANDONED Continuation of Ser. No. US

1995-517051, filed on 21 Aug 1995, ABANDONED

Continuation-in-part of Ser. No. US 1994-305526, filed on 13 Sep 1994, ABANDONED Continuation-in-part of Ser. No. US 1997-816065, filed on 11 Mar 1997, ABANDONED

DATE NUMBER -----

PRIORITY INFORMATION:

US 1997-40660P 19970311 (60) US 1996-13119P 19960311 (60)

DOCUMENT TYPE:

Utility

FILE SEGMENT:

APPLICATION

LEGAL REPRESENTATIVE: BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100,

WASHINGTON, DC, 20001

NUMBER OF CLAIMS: EXEMPLARY CLAIM:

LINE COUNT:

6892

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Provided are novel benzothiepines, derivatives, and analogs thereof; pharmaceutical compositions containing them; and methods of using these compounds and compositions in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions such as those associated with atherosclerosis or hypercholesterolemia, in mammals. Also provided are compositions and methods for combination therapy employing ileal bile acid transport inhibitors and HMG Co-A reductase inhibitors for the treatment of hyperlipidemic conditions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 2 OF 12 USPATFULL on STN

ACCESSION NUMBER:

2004:178975 USPATFULL

TITLE:

Application of intestinal biliary acid reuptake inhibitors for the prevention and treatment of

alzheimer's disease

INVENTOR(S):

Canton, Thierry, Etrechy, FRANCE Pradier, Laurent, Verrieres, FRANCE

Benavides, Jesus, Chatenay Malabry, FRANCE

Heuer, Hubert, Schwabenheim, GERMANY, FEDERAL REPUBLIC

Schaefer, Hans-Ludwig, Hochheim, GERMANY, FEDERAL

REPUBLIC OF

PATENT ASSIGNEE(S):

Aventis Pharma S.A., Antony, FRANCE (non-U.S.

corporation)

NUMBER KIND DATE US 2004138145 A1 20040715 PATENT INFORMATION: US 2003-734787 A1 20031212 (10) APPLICATION INFO .:

US 2003-455354P 20030317 (60)

NUMBER _____ FR 2002-15722 20021212

PRIORITY INFORMATION:

DATE

DOCUMENT TYPE: Utility APPLICATION FILE SEGMENT: LEGAL REPRESENTATIVE: ROSS J. OEHLER, AVENTIS PHARMACEUTICALS INC., ROUTE 202-206, MAIL CODE: D303A, BRIDGEWATER, NJ, 08807 NUMBER OF CLAIMS: 1 EXEMPLARY CLAIM: NUMBER OF DRAWINGS: 4 Drawing Page(s) 682 LINE COUNT: CAS INDEXING IS AVAILABLE FOR THIS PATENT. The subject of the invention is the application of intestinal biliary acid reuptake inhibitors for the prevention and treatment of Alzheimer's disease, where appropriate, in combination with an HMG-CoA reductase inhibitor, a cholesterol uptake inhibitor, a cholesterol synthesis inhibitor or an APP secretase inhibitor. CAS INDEXING IS AVAILABLE FOR THIS PATENT. L15 ANSWER 3 OF 12 USPATFULL on STN 2004:145088 USPATFULL ACCESSION NUMBER: Combination therapy for the prophylaxis and treatment TITLE: of hyperlipidemic conditions and disorders Keller, Bradley T., Chesterfield, MO, UNITED STATES INVENTOR(S): Tremont, Samuel J., St. Louis, MO, UNITED STATES Glenn, Kevin C., Maryland Heights, MO, UNITED STATES Manning, Robert E., St. Louis, MO, UNITED STATES G.D. SEARLE LLC, Chicago, IL, 60680 (U.S. corporation) PATENT ASSIGNEE(S): DATE KIND NUMBER ----------------US 2004110761 A1 20040610 US 2003-611942 A1 20030703 (10) PATENT INFORMATION: APPLICATION INFO.: Continuation of Ser. No. US 2001-802313, filed on 8 Mar RELATED APPLN. INFO.: 2001, ABANDONED DATE NUMBER -----US 2000-188378P 20000310 (60) US 2000-188361P 20000310 (60) PRIORITY INFORMATION: Utility DOCUMENT TYPE: APPLICATION LEGAL REPRESENTATIVE: BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100, FILE SEGMENT: WASHINGTON, DC, 20001 89 NUMBER OF CLAIMS: 1 EXEMPLARY CLAIM: 4655 LINE COUNT: CAS INDEXING IS AVAILABLE FOR THIS PATENT. Novel methods and combinations for the treatment and/or prophylaxis of a AΒ hyperlipidernic condition or disorder in a subject, wherein the methods comprise the administration of one or more HMG Co-A reductase inhibitors and one or more ASBT inhibitors selected from the specific group of compounds described herein, and the combinations comprise one or more HMG Co-A reductase inhibitors and one or more of said apical sodium

co-dependent bile acid transport inhibitors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 4 OF 12 USPATFULL on STN

ACCESSION NUMBER:

2004:108245 USPATFULL

TITLE:

INVENTOR(S):

Method for the preparation of tetrahydrobenzothiepines

Babiak, Kevin A., Evanston, IL, UNITED STATES Carpenter, Andrew, Zebulon, NC, UNITED STATES Chou, Shine, St. Louis, MO, UNITED STATES Colson, Pierre-Jean, Skokie, IL, UNITED STATES Farid, Payman, Vernon Hills, IL, UNITED STATES

Hett, Robert, Aarau, SWITZERLAND

Huber, Christian H., Skokie, IL, UNITED STATES

Koeller, Kevin J., Maryland Heights, MO, UNITED STATES

Lawson, Jon P., Glencoe, MO, UNITED STATES Li, James, Pennington, NJ, UNITED STATES

Mar, Eduardo K., Northbrook, IL, UNITED STATES
Miller, Lawrence M., Des Plaines, IL, UNITED STATES
Orlovski, Vladislav, Wheeling, IL, UNITED STATES
Peterson, James C., Manchester, MO, UNITED STATES
Pozzo, Mark J., Chesterfield, MO, UNITED STATES
Przybyla, Claire A., Des Plains, IL, UNITED STATES
Tremont, Samuel J., St. Louis, MO, UNITED STATES

Trivedi, Jay S., Skokie, IL, UNITED STATES

Wagner, Grace M., Webster Groves, MO, UNITED STATES Weisenburger, Gerald A., Evanston, IL, UNITED STATES

Zhi, Benxin, Newbury Park, CA, UNITED STATES

PATENT ASSIGNEE(S):

G.D. SEARLE, LLC, Chicago, IL (U.S. corporation)

NUMBER KIND DATE

PATENT INFORMATION:
APPLICATION INFO.:

US 2004082647 A1 20040429 US 2003-419266 A1 20030421 (10)

RELATED APPLN. INFO.:

Division of Ser. No. US 2001-802279, filed on 8 Mar

2001, GRANTED, Pat. No. US 6586434

NUMBER DATE

PRIORITY INFORMATION:

US 2000-188361P 20000310 (60)

DOCUMENT TYPE:

APPLICATION

FILE SEGMENT:

Utility

LEGAL REPRESENTATIVE:

BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100,

WASHINGTON, DC, 20001

NUMBER OF CLAIMS:

336

EXEMPLARY CLAIM:

1
15 Drawing Page(s)

NUMBER OF DRAWINGS: LINE COUNT:

5427

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Among its several embodiments, the present invention provides an improved process for the preparation of tetrahydrobenzothiepine-1,1-dioxide compounds; the provision of a process for preparing a diastereomeric mixture of tetrahydrobenzothiepine-1,1-dioxide compounds from a single diastereomer of such compounds; the provision of a process for the preparation of 3-bromo-2-substituted propional dehyde compounds; and the provision of a process for the preparation of

3-thio-2-substituted propionaldehyde compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 5 OF 12 USPATFULL on STN

ACCESSION NUMBER:

2004:88896 USPATFULL

TITLE:

Novel mono- and di-fluorinated benzothiepine compouds as inhibitors of apical sodium co-dependent bile acid

transport (ASBT) and taurocholate uptake

INVENTOR(S):

Tremont, Samuel J., St. Louis, MO, UNITED STATES Koeller, Kevin J., Maryland Heights, MO, UNITED STATES

PATENT ASSIGNEE(S):

G.D. SEARLE, LLC, St. Louis, MO, UNITED STATES (U.S.

corporation)

NUMBER KIND DATE US 2004067872 A1 20040408 US 6740663 B2 20040525 PATENT INFORMATION: US 2002-286987 A1 20021104 (10)

APPLICATION INFO .:

NUMBER DATE _____

DOCUMENT TYPE:

PRIORITY INFORMATION: US 2001-330892P 20011102 (60) Utility

FILE SEGMENT:

APPLICATION

LEGAL REPRESENTATIVE: BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100,

WASHINGTON, DC, 20001

150 NUMBER OF CLAIMS: EXEMPLARY CLAIM: 13074

LINE COUNT:

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Mono-fluorinated and di-fluorinated benzothiepine apical sodium co-dependent bile acid transport (ASBT) inhibitors are disclosed together with methods of making the same, methods of using the same to treat hyperlipidemic conditions as well as pharmaceutical compositions containing the same compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 6 OF 12 USPATFULL on STN

ACCESSION NUMBER:

2004:19499 USPATFULL

TITLE:

Novel benzothiepines having activity as inhibitors of

lleal bile acid transport and taurocholate uptake Lee, Len F., St. Charles, MO, UNITED STATES

INVENTOR(S):

Banerjee, Shyamal C., Chesterfield, MO, UNITED STATES Huang, Horng-Chih, Chesterfield, MO, UNITED STATES

Li, Jinglin J., Chesterfield, MO, UNITED STATES Miller, Raymond E., Fairview Heights, IL, UNITED STATES

Reitz, David B., Chesterfield, MO, UNITED STATES Tremont, Samuel J., St. Louis, MO, UNITED STATES G.D. Searle & Co., Skokie, IL, UNITED STATES, 60067

PATENT ASSIGNEE(S):

(U.S. corporation)

NUMBER KIND DATE US 2004014803 A1 20040122 PATENT INFORMATION:

APPLICATION INFO .: RELATED APPLN. INFO.:

US 2002-68297 20020208 (10) A1Division of Ser. No. US 2001-828968, filed on 9 Apr 2001, GRANTED, Pat. No. US 6387924 Continuation-in-part of Ser. No. US 2001-816065, filed on 26 Mar 2001, PENDING Continuation-in-part of Ser. No. US 2001-831284, filed on 4 May 2001, PENDING Continuation of Ser. No. US 1995-517051, filed on 21 Aug 1995, ABANDONED Continuation-in-part of Ser. No. US 1994-305526, filed on 13 Sep 1994, ABANDONED

> DATE NUMBER

PRIORITY INFORMATION:

_____ US 1996-13119P 19960311 (60)

DOCUMENT TYPE:

Utility

FILE SEGMENT:

APPLICATION

LEGAL REPRESENTATIVE: BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100,

WASHINGTON, DC, 20001

NUMBER OF CLAIMS: EXEMPLARY CLAIM:

346 1

LINE COUNT:

12747

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Provided are novel benzothiepines, derivatives, and analogs thereof; pharmaceutical compositions containing them; and methods of using these compounds and compositions in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions such as those associated with atherosclerosis or hypercholesterolemia, in mammals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 7 OF 12 USPATFULL on STN

ACCESSION NUMBER:

2003:335528 USPATFULL

TITLE:

INVENTOR(S):

Method for the preparation of tetrahydrobenzothiepines Babiak, Kevin A., Evanston, IL, UNITED STATES Carpenter, Andrew, Zebulon, NC, UNITED STATES Chou, Shine, St. Louis, MO, UNITED STATES Colson, Pierre-Jean, Skokie, IL, UNITED STATES Farid, Payman, Vernon Hills, IL, UNITED STATES Hett, Robert, Aarau, SWITZERLAND Huber, Christian H., Skokie, IL, UNITED STATES Koeller, Kevin J., Richmond Heights, MD, UNITED STATES Lawson, Jon P., Glencoe, MO, UNITED STATES Li, James, Hopewell Township, NJ, UNITED STATES Mar, Eduardo K., Northbrook, IL, UNITED STATES Miller, Lawrence M., Des Plaines, IL, UNITED STATES Orlovski, Vladislav, Wheeling, IL, UNITED STATES Peterson, James C., Manchester, MO, UNITED STATES Pozzo, Mark J., Chesterfield, MO, UNITED STATES Przybyla, Claire A., Des Plaines, IL, UNITED STATES Tremont, Samuel J., St. Louis, MO, UNITED STATES Trivedi, Jay S., Skokie, IL, UNITED STATES Wagner, Grace M., Webster Groves, MO, UNITED STATES Weisenburger, Gerald A., Des Plaines, IL, UNITED STATES Zhi, Benxin, Hoffman Estates, IL, UNITED STATES

KIND DATE NUMBER

US 2003236406 20031225 A1 PATENT INFORMATION: A120021223 (10) US 2002-204826 APPLICATION INFO .: 20010308 WO 2001-US7421

Utility DOCUMENT TYPE: APPLICATION FILE SEGMENT:

Banner & Witcoff, Eleventh Floor, 1001 G Street NW, LEGAL REPRESENTATIVE:

Washington, DC, 20001-4597

336 NUMBER OF CLAIMS: EXEMPLARY CLAIM: 1

11 Drawing Page(s) NUMBER OF DRAWINGS:

5434 LINE COUNT:

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Among its several embodiments, the present invention provides an improved process for the preparation of tetrahydrobenzothiepine-1,1dioxide compounds; the provision of a process for preparing a diastereomeric mixture of tetrahydrobenzothiepine-1,1-dioxide compounds from a single diastereomer of such compounds; the provision of a process for the preparation of 3-bromo-2-substituted propionaldehyde compounds; and the provision of a process for the preparation of ##STR1## ##STR2## 3-thio-2-substituted propionaldehyde compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 8 OF 12 USPATFULL on STN

2003:330619 USPATFULL ACCESSION NUMBER:

TITLE:

Combination therapy for the prophylaxis and treatment

of hyperlipidemic conditions and disorders

Keller, Bradley T, Chesterfield, MO, UNITED STATES INVENTOR(S):

Tremont, Samuel J, St Louis, MO, UNITED STATES Glenn, Kevin C, Maryland Heights, MO, UNITED STATES

Manning, Robert E, St Louis, MO, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION: APPLICATION INFO.:	US 2003232834 US 2002-204672 WO 2001-US7505	A1 A1	20031218 20021126 20010308	(10)

DOCUMENT TYPE: Utility APPLICATION FILE SEGMENT:

BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100, LEGAL REPRESENTATIVE:

WASHINGTON, DC, 20001

89 NUMBER OF CLAIMS: EXEMPLARY CLAIM:

5 Drawing Page(s) NUMBER OF DRAWINGS:

4647 LINE COUNT:

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

A method of treatment of a host with a cellular proliferative disease, comprising contacting the host with a cephalotaxine and an antiproliferative agent, each in an amount sufficient to modulate said cellular proliferative disease, is described. In some embodiments, the cephalotaxine comprises homoharringtonine (cephalotaxine, 4-methyl-2-hydroxy-2-(4-hydroxy-4-methyl pentyl) butanediocate ester). Antiproliferative agents of the invention comprise alkylating agents, intercalating agents, metal coordination complexes, pyrimidine nucleosides, purine nucleosides, inhibitors of nucleic acid associated enzymes and proteins, and agents affecting structural proteins and

> 571-272-2528 Shears Searcher :

cytoplasmic enzymes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 9 OF 12 USPATFULL on STN

ACCESSION NUMBER: 2002:119900 USPATFULL

Combination therapy for the prophylaxis and treatment TITLE:

of hyperlipidemic conditions and disorders

Keller, Bradley T., Chesterfield, MO, UNITED STATES INVENTOR(S): Tremont, Samuel J., St. Louis, MO, UNITED STATES Glenn, Kevin C., Maryland Heights, MO, UNITED STATES

Manning, Robert E., St. Louis, MO, UNITED STATES

NUMBER KIND DATE US 2002061888 A1 20020523 US 2001-802313 A1 20010308 (9) PATENT INFORMATION: APPLICATION INFO.:

NUMBER DATE ______

PRIORITY INFORMATION: US 2000-188378P 20000310 (60) US 2000-188361P 20000310 (60)

Utility DOCUMENT TYPE:

APPLICATION FILE SEGMENT:

LEGAL REPRESENTATIVE: BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100,

WASHINGTON, DC, 20001

89 NUMBER OF CLAIMS: EXEMPLARY CLAIM:

INVENTOR(S):

NUMBER OF DRAWINGS: 5 Drawing Page(s)

4626 LINE COUNT:

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Novel methods and combinations for the treatment and/or prophylaxis of a hyperlipidemic condition or disorder in a subject, wherein the methods comprise the administration of one or more HMG Co-A reductase inhibitors and one or more ASBT inhibitors selected from the specific group of compounds described herein, and the combinations comprise one or more MIG Co-A reductase inhibitors and one or more of said apical sodium co-dependent bile acid transport inhibitors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 10 OF 12 USPATFULL on STN

2002:55165 USPATFULL

ACCESSION NUMBER:

Method for the preparation of tetrahydrobenzothiepines TITLE:

Babiak, Kevin A., Evanston, IL, UNITED STATES Carpenter, Andrew, Zebulon, NC, UNITED STATES
Chou, Shine, St. Louis, MO, UNITED STATES

Colson, Pierre-Jean, Skokie, IL, UNITED STATES Farid, Payman, Vernon Hills, IL, UNITED STATES

Hett, Robert, Aarau, SWITZERLAND

Huber, Christian H., Skokie, IL, UNITED STATES

Koeller, Kevin J., Maryland Heights, MO, UNITED STATES

Lawson, Jon P., Glencoe, MO, UNITED STATES Li, James, Pennington, NJ, UNITED STATES

Mar, Eduardo K., Northbrook, IL, UNITED STATES

Miller, Lawrence M., Des Plaines, IL, UNITED STATES

Orlovski, Vladislav, Wheeling, IL, UNITED STATES Peterson, James C., Manchester, MO, UNITED STATES Pozzo, Mark J., Chesterfield, MO, UNITED STATES
Przybyla, Claire A., Des Plaines, IL, UNITED STATES Tremont, Samuel J., St. Louis, MO, UNITED STATES Trivedi, Jay S., Skokie, IL, UNITED STATES Wagner, Grace M., Webster Groves, MO, UNITED STATES Weisenburger, Gerald A., Evanston, IL, UNITED STATES Zhi, Benxin, Newbury Park, CA, UNITED STATES

NUMBER KIND DATE US 2002032329 A1 20020314 PATENT INFORMATION: US 6586434 B2 20030701 US 2001-802279 A1 20010308 (9) APPLICATION INFO.:

NUMBER DATE

US 2000-188361P 20000310 (60) PRIORITY INFORMATION:

DOCUMENT TYPE: Utility APPLICATION FILE SEGMENT:

LEGAL REPRESENTATIVE: BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100,

WASHINGTON, DC, 20001

NUMBER OF CLAIMS: 336 EXEMPLARY CLAIM: 1

11 Drawing Page(s) NUMBER OF DRAWINGS:

5437 LINE COUNT:

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Among its several embodiments, the present invention provides an improved process for the preparation of tetrahydrobenzothiepine-1,1dioxide compounds; the provision of a process for preparing a diastereomeric mixture of tetrahydrobenzothiepine-1,1-dioxide compounds from a single diastereomer of such compounds; the provision of a process for the preparation of 3-bromo-2-substituted propional dehyde compounds; and the provision of a process for the preparation of 3-thio-2-substituted propionaldehyde compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 11 OF 12 USPATFULL on STN

2001:121499 USPATFULL ACCESSION NUMBER:

Combination therapy employing ileal bile acid transport TITLE:

inhibiting benzothiepines and HMG Co-A reductase

inhibitors

Keller, Bradley T., Chesterfield, MO, United States INVENTOR(S):

Glenn, Kevin C., Maryland Heights, MO, United States Manning, Robert E., St. Louis, MO, United States

G. D. Searle & Co., Skokie, IL, United States (U.S.

PATENT ASSIGNEE(S): corporation)

NUMBER KIND DATE ______ US 6268392 B1 20010731 US 1998-37308 19980309 PATENT INFORMATION: 19980309 (9) APPLICATION INFO .:

Continuation-in-part of Ser. No. US 1997-831284, filed RELATED APPLN. INFO.: on 31 Mar 1997, now abandoned Continuation of Ser. No.

US 1995-517051, filed on 21 Aug 1995 Continuation-in-part of Ser. No. US 1994-305526, filed on 12 Sep 1994 Continuation-in-part of Ser. No. US 1997-816065, filed on 11 Mar 1997

NUMBER	DATE
	_

PRIORITY INFORMATION:

US 1997-40660P 19970311 (60) US 1996-13119P 19960311 (60)

DOCUMENT TYPE:

Utility GRANTED

FILE SEGMENT: PRIMARY EXAMINER:

Lambkin, Deborah C.

LEGAL REPRESENTATIVE: NUMBER OF CLAIMS:

Williams, Scott A. 49

EXEMPLARY CLAIM:

1 7970

LINE COUNT:

CAS INDEXING IS AVAILABLE FOR THIS PATENT. Provided are novel benzothiepines, derivatives, and analogs thereof;

pharmaceutical compositions containing them; and methods of using these compounds and compositions in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions such as those associated with atherosclerosis or hypercholesterolemia, in mammals. Also provided are compositions and methods for combination therapy employing ileal bile acid transport inhibitors and EG Co-A reductase inhibitors for the treatment of hyperlipidemic conditions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 12 OF 12 USPATFULL on STN

ACCESSION NUMBER:

2000:109998 USPATFULL

TITLE:

Substituted 5-aryl-benzothiepines having activity as

inhibitors of ileal bile acid transport and

taurocholate uptake

INVENTOR(S):

Lee, Len F., St. Charles, MO, United States

Banerjee, Shyamal C., Chesterfield, MO, United States Huang, Horng-Chih, Chesterfield, MO, United States Li, Jinglin J., Chesterfield, MO, United States

Miller, Raymond E., Fairview Heights, IL, United States

Reitz, David B., Chesterfield, MO, United States Tremont, Samuel J., St. Louis, MO, United States G.D. Searle and Company, Skokie, IL, United States

PATENT ASSIGNEE(S): (U.S. corporation)

> KIND DATE NUMBER

PATENT INFORMATION: APPLICATION INFO.: RELATED APPLN. INFO.:

20000822 US 6107494 19990324 (9) US 1999-275463

Continuation-in-part of Ser. No. US 1998-109551, filed on 2 Jul 1998 which is a continuation-in-part of Ser. No. US 1997-816065, filed on 11 Mar 1997, now abandoned And a continuation-in-part of Ser. No. US 1997-831284, filed on 31 Mar 1997, now abandoned which is a continuation of Ser. No. US 1995-517051, filed on 21

Aug 1995, now abandoned which is a continuation-in-part of Ser. No. US 1994-305526, filed on 12 Sep 1994, now

abandoned

571-272-2528 Searcher : Shears

DATE NUMBER

PRIORITY INFORMATION:

US 1996-13119P

19960311 (60)

DOCUMENT TYPE:

Utility

FILE SEGMENT:

Granted

PRIMARY EXAMINER:

Lambkin, Deborah C.

LEGAL REPRESENTATIVE:

Senniger, Powers, Leavitt & Roedel

NUMBER OF CLAIMS: EXEMPLARY CLAIM:

19 1

LINE COUNT:

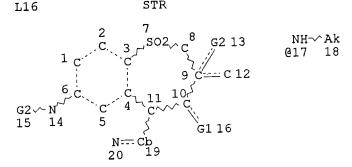
9643

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Provided are novel benzothiepines, derivatives, and analogs thereof; pharmaceutical compositions containing them; and methods of using these compounds and compositions in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions such as those associated with atherosclerosis or hypercholesterolemia, in mammals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

(FILE 'MARPAT' ENTERED AT 09:31:41 ON 26 AUG 2004) STR



VAR G1=H/OH/NH/17 VAR G2=ME/ET/I-PR/N-PR/I-BU/N-BU/S-BU/T-BU NODE ATTRIBUTES: DEFAULT MLEVEL IS ATOM

MLEVEL IS CLASS AT 18 19

IS LOC AT 18 GGCAT

GGCAT IS UNS AT 19

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:

ECLEVEL IS LIM ON ALL NODES ALL RING(S) ARE ISOLATED

14 SEA FILE=MARPAT SSS FUL L16 (MODIFIED ATTRIBUTES)

13 SEA FILE=MARPAT ABB=ON PLU=ON L18/COMPLETE only iterations

that are complete L18 L19

571-272-2528 Searcher : Shears

L19 ANSWER 1 OF 13 MARPAT COPYRIGHT 2004 ACS on STN 141:17641 MARPAT ACCESSION NUMBER: Methods and compositions for the prevention and TITLE: treatment of Alzheimer's disease with intestinal bile acid reuptake inhibitors Aventis Pharma SA, Fr. PATENT ASSIGNEE(S): Fr. Demande, 25 pp. SOURCE: CODEN: FRXXBL Patent DOCUMENT TYPE: French LANGUAGE: FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION: APPLICATION NO. DATE KIND DATE PATENT NO. _____ ______ ____ FR 2848452 A1 20040618 FR 2002-15722 20021212 WO 2004062652 A1 20040729 WO 2003-FR3654 20031210 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG US 2003-734787 20031212 US 2004138145 A1 20040715 20021212 FR 2002-15722 PRIORITY APPLN. INFO.: US 2003-455354P 20030317 The invention describe the application of the intestinal biliary acid AB reuptake inhibitors for the prevention and the treatment of Alzheimer's disease, alone or in conjunction with an HMG-CoA reductase inhibitor , a cholesterol uptake inhibitor, a cholesterol synthesis inhibitor or an inhibitor of APP secretases. ICM A61K031-444 IC ICS A61K031-38; A61P025-28 1-11 (Pharmacology) CC bile acid reuptake inhibitors intestine Alzheimers disease treatment prevention Intestine IT (biliary acid reuptake; methods and compns. for prevention and treatment of Alzheimer's disease with intestinal bile acid reuptake inhibitors) Alzheimer's disease IT Anti-Alzheimer's agents Human (methods and compns. for prevention and treatment of Alzheimer's disease with intestinal bile acid reuptake inhibitors) Bile acids ITRL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (reuptake inhibitors; methods and compns. for prevention and treatment of Alzheimer's disease with intestinal bile acid reuptake inhibitors) Biological transport IT

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(reuptake, bile acid, inhibitors of; methods and compns. for prevention
       and treatment of Alzheimer's disease with intestinal bile acid reuptake
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     Biological transport
IT
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        methods and compns. for prevention and treatment of Alzheimer's disease
        with intestinal bile acid reuptake inhibitors)
                                   158736-49-3, \beta-Secretase
    9028-35-7, HMG-CoA reductase
IT
     338454-52-7, Y Secretase
    RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (inhibitor, in conjunction with treatment; methods and compns. for
        prevention and treatment of Alzheimer's disease with intestinal bile
        acid reuptake inhibitors)
     252047-40-8
                  263562-55-6
IT
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (methods and compns. for prevention and treatment of Alzheimer's
        disease with intestinal bile acid reuptake inhibitors)
     57-88-5, Cholesterol, biological studies
IT
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (uptake and synthesis inhibitors, in conjunction with treatment;
        methods and compns. for prevention and treatment of Alzheimer's disease
        with intestinal bile acid reuptake inhibitors)
                               THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS
REFERENCE COUNT:
                         11
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
L19 ANSWER 2 OF 13 MARPAT COPYRIGHT 2004 ACS on STN
                         140:111291 MARPAT
ACCESSION NUMBER:
                         Preparation of substituted 5-aryl-benzothiepines as
TITLE:
                         ileal bile acid transport and taurocholate uptake
                         inhibitors
                         Lee, Len F.; Banerjee, Shyamal C.; Huang, Horng Chih;
INVENTOR(S):
                         Li, Jinglin J.; Miller, Raymond E.; Reitz, David B.;
                         Tremont, Sanuel J.
                         G.D. Searle and Co., USA
PATENT ASSIGNEE(S):
                         U.S. Pat. Appl. Publ., 235 pp., Cont.-in-part of U.S.
SOURCE:
                         Ser. No. 831,284.
                         CODEN: USXXCO
                         Patent
DOCUMENT TYPE:
                         English
TANGUAGE:
FAMILY ACC. NUM. COUNT:
PATENT INFORMATION:
                                           APPLICATION NO. DATE
                     KIND DATE
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                                                            20020208
                                           US 2002-68297
                            20040122
     US 2004014803
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                                           EP 2004-10088
                                                            19970311
                      A1
                           20040728
     EP 1440972
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI
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                      A1 20030911
      US 2003171426
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Searcher : Shears 571-272-2528

US 1994-305526

19940913

20031104

В2

US 6642268

PRIORITY APPLN. INFO.:

US	1995-517051	19950821
US	1996-13119P	19960311
US	1997-816065	19970311
US	2001-828968	20010409
US	2001-831284	20010504
ΑU	1997-23266	19970311
ΕP	1997-915976	19970311
US	1997-40660P	19970311
US	1997-831284	19970331
US	1997-68170P	19971219
US	1998-109551	19980702
US	1999-275463	19990324
US	1999-443403	19991119
US	2000-676466	20000929

GI

$$(R?) q \xrightarrow{\begin{array}{c} (O)_{n} \\ R^{7} \\ S \end{array} \xrightarrow{\begin{array}{c} R^{8} \\ R^{2} \\ R^{3} \end{array}}$$

The title compds. (I) [wherein q = 1-4; n = 0-2; R1, R2 = H, AΒ (un) substituted (halo) alkyl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy(alkyl), dialkylamino, alkylthio, (polyalkyl)aryl, or cycloalkyl; or R1 and R2 taken together with the atoms to which they are attached = cycloalkyl; R3, R4 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, or SO3R9; R9, R10 = H, (cyclo) alkyl, alkenyl, alkynyl, aryl(alkyl), acyl, heterocyclyl, or ammoniumalkyl; or R3 and R4 together = :0, :NOR11, :S, :NNR11R12, :NR9, or :CR11R12; R11, R12 = H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), heterocyclyl, carboxylalkyl, carboalkoxyalkyl, cyanoalkyl, OR9, NR9R10, SR9, S(0)R9, SO2R9, SO3R9, CO2R9, CN, halo, oxo, or CONR9R10; R5, R6 = H, alkyl, aryl, etc.; R7, R8 = H, alkyl; Rx = H, (un) substituted (cyclo)alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl(alkyl), halo(alkyl), (quaternary) heterocyclyl, (quaternary) heteroaryl, polyether, alkoxy, amino, alkylthio, NO2, carboxy, carbamido, etc.] were prepared for the prophylaxis and treatment of hyperlipidemic conditions, such as those associated with atherosclerosis or hypercholesterolemia.

Ι

Thus,

```
KOBu-t was added to a solution of 2-((2-benzyl-5-
    methoxyphenylsulfonyl)methyl)-2-ethylhexanal (preparation given) and dry THF
    cooled to -1.6°C to give, after workup, II and III (96% combined
    yield). The isomers were separated upon recrystn. II inhibited
IBAT-mediated
    uptake of [14C]-taurocholate in H14 cells with an IC50 of 0.1 \mu M and
    reduced serum cholesterol from 143 mg (7%) to 126 mg (2%) compared to
    control in cholesterol-fed hamsters in a 14-day test. In vitro
    taurocholate uptake assay data are included for nearly 600 compds. of the
    invention.
    C07D337-16; A61K031-38
TC
NCL 514431000
    27-21 (Heterocyclic Compounds (One Hetero Atom))
CC
     Section cross-reference(s): 1, 63
    arylbenzothiepine prepn ileal bile acid transport inhibitor; benzothiepine
    prepn taurocholate uptake inhibitor; hypolipemic antiatherosclerotic
ST
     anticholesterolemic arylbenzothiepine prepn
    Antiarteriosclerotics
        (antiatherosclerotics; preparation of substituted 5-aryl-benzothiepines
IT
by
        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
     Lipids, biological studies
ΙT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (hyperlipidemia, treatment of; preparation of substituted
        5-aryl-benzothiepines by cyclization of 2-((2-benzyl- and
        2-benzoylphenylthio)methyl)alkanals as ileal bile acid transport and
        taurocholate uptake inhibitors)
     Bile acids
ΙT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (inhibition of ileal; preparation of substituted 5-aryl-benzothiepines by
        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
     Anticholesteremic agents
ΙT
     Human
     Hypolipemic agents
        (preparation of substituted 5-aryl-benzothiepines by cyclization of
        2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile
        acid transport and taurocholate uptake inhibitors)
IT Atherosclerosis
     Hypercholesterolemia
        (treatment of; preparation of substituted 5-aryl-benzothiepines by
        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
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     RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic
      preparation); THU (Therapeutic use); BIOL (Biological study); PREP
      (Preparation); RACT (Reactant or reagent); USES (Uses)
         (hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by
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cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
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      (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
      (Uses)
         (hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by
         cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
         ileal bile acid transport and taurocholate uptake inhibitors)
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    (hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by
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    ileal bile acid transport and taurocholate uptake inhibitors)
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 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
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(Uses)
        (hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by
        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
                                           5437-45-6P, Benzyl 2-bromoacetate
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     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
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        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
                                              57-88-5, Cholesterol, biological
     56-41-7, L-Alanine, biological studies
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                         9027-63-8, Cholesterol acyl transferase
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         (preparation of substituted 5-aryl-benzothiepines by cyclization of
        2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile
        acid transport and taurocholate uptake inhibitors)
     197372-68-2P
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         (preparation of substituted 5-aryl-benzothiepines by cyclization of
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         acid transport and taurocholate uptake inhibitors)
      647859-02-7P
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     preparation); THU (Therapeutic use); BIOL (Biological study); PREP
      (Preparation); RACT (Reactant or reagent); USES (Uses)
         (preparation of substituted 5-aryl-benzothiepines by cyclization of
         2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile
         acid transport and taurocholate uptake inhibitors)
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      RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
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(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
        (preparation of substituted 5-aryl-benzothiepines by cyclization of
       2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile
       acid transport and taurocholate uptake inhibitors)
     28994-41-4, 2-Hydroxydiphenylmethane
IT
    RL: RCT (Reactant); RACT (Reactant or reagent)
        (preparation of substituted 5-aryl-benzothiepines by cyclization of
        2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile
        acid transport and taurocholate uptake inhibitors)
     51-45-6, Histamine, reactions 55-98-1, Busulfan 68-12-2, reactions
IT
                                                   110-86-1, Pyridine,
                          106-41-2, 4-Bromophenol
     100-66-3, reactions
                110-91-8, Morpholine, reactions 111-24-0, 1,5-Dibromopentane
     reactions
     111-96-6, 2-Methoxyethyl ether 123-12-6, N,N,N',N'-Tetraethyl
                        123-75-1, Pyrrolidine, reactions 131-57-7,
     diethylenetriamine
     2-Hydroxy-4-methoxybenzophenone 138-60-3, Chelidamic acid
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     3-Methoxyphenol 150-76-5, 4-Methoxyphenol 280-57-9,
     1,4-Diazabicyclo[2.2.2]octane 352-11-4, 4-Fluorobenzyl chloride
                                                     504-63-2, 1,3-Propanediol
     371-41-5, 4-Fluorophenol 503-29-7, Azetidine
                623-25-6, \alpha, \alpha'-Dichloro-p-xylene
                                                 628-11-5,
     596-75-8
     3-Chloropropyl chloroformate 628-77-3, 1,5-Diiodopentane
                         705-29-3, 3-(Trifluoromethyl)benzyl chloride
     4-Methoxythiophenol
     824-98-6, 3-Methoxybenzyl chloride 869-24-9, 2-Diethylaminoethyl
                             922-63-4, 2-Ethylacrolein
                                                         1120-71-4,
     chloride hydrochloride
                                                          1680-78-0,
                          1633-83-6, 1,4-Butane sultone
     1,3-Propane sultone
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     2-Ethyl-2-(hydroxymethyl)hexanal
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     Cyclohexanecarboxaldehyde
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     2516-96-3, 2-Chloro-5-nitrobenzoic acid
                           3099-28-3, 2,6-Bis(chloromethyl)pyridine
     Difluorobenzaldehyde
     4509-90-4, 5-Bromovaleroyl chloride 4521-31-7 4724-56-5
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     Bis(2-bromoethyl)ether 5469-66-9, 1,3-Propanediol di-p-tosylate
     6290-05-7 7136-51-8, N,N,N',N'-Tetraethyl 1,6-hexanediamine
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     1,2-Bis(2-iodoethoxy)ethane 41602-50-0, N-(Chloroacetyl)glycine ethyl
             60343-28-4, Benzyl 5-bromovalerate
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        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
L19 ANSWER 3 OF 13 MARPAT COPYRIGHT 2004 ACS on STN
                         138:385315 MARPAT
ACCESSION NUMBER:
                         Mono- and di-fluorinated benzothiepines as inhibitors
TITLE:
                         of apical sodium co-dependent bile acid transport
                          (ASBT) and taurocholate uptake for treating
                         hyperlipidemic conditions and methods for preparation
                         Koeller, Kevin J.; Tremont, Samuel J.
 INVENTOR(S):
                         G.D. Searle and Co., USA
 PATENT ASSIGNEE(S):
                         PCT Int. Appl., 589 pp.
 SOURCE:
                         CODEN: PIXXD2
 DOCUMENT TYPE:
                         Patent
                          English
 LANGUAGE:
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FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT	NO.		KI	ND I	DATE			Al	PPLI	CATIO	ON NO	o. 	DATE			
WO 200 W:	AE, CO, GM, LS, PL, UA, RU,	AG, CR, HR, LT, PT, UG, TJ, GM,	AL, CU, HU, LU, RO, US, TM KE,	AM, CZ, ID, LV, RU, UZ,	AT, DE, IL, MA, SD, VC, MW, DK.	AU, DK, IN, MD, SE, VN, MZ, EE,	AZ, DM, IS, MG, SG, YU, SD, ES,	BA, DZ, JP, MK, SI, ZA,	BB, EC, KE, MN, SK, ZM,	BG, EE, KG, MW, SL, ZW,	BR, ES, KP, MX, TJ, AM, UG, GR,	BY, FI, KR, MZ, TM, AZ,	BZ, GB, KZ, NO, TN, BY,	CA, GD, LC, NZ, TR, KG,	LK, OM, TT, KZ, BE, MC,	LR, PH, TZ, MD, BG, NL,
US 200 US 674 EP 144 R: PRIORITY AN	NE, 040678 10663 18546 AT, IE,	SN, 72 BE, SI,	TD, A B A CH, LT,	TG 1 2 1 DE,	2004 2004 2004 DK,	0408 0525 0825 ES,	FR,	E GB, CY,	S 20 P 20 GR, AL, S 20	02-2 02-7 IT, TR, 01-3	8698 7871 LI, BG, 3089	7 1 LU, CZ, 2P	2002 2002	1104 1104 SE, SK 1102	MC,	

GΙ

Mono-fluorinated and di-fluorinated benzothiepine apical Na co-dependent bile acid transport (ASBT) inhibitors (shown as I; variables defined below; no specific examples are included) are disclosed together with methods of making the same, methods of using the same to treat hyperlipidemic conditions as well as pharmaceutical compns. containing the same compds. For I: X = F, X' = H, F; n = 0-2; m = 0-4; R2A and R2B = H and hydrocarbyl; R3A, R3B, R5A, and R5B = H, alkyl, cycloalkyl, alkenyl, alkynyl, heterocyclyl, quaternary heterocyclyl, oxo, aryl-R5, -OR9, -NR9R10, -SR9, -S(O)R9, -SO2R9, and -SO3R9; R9 and R10 = H, hydrocarbyl, amino, and hydrocarbylamino. R5 = H, hydrocarbyl, heterocyclyl, quaternary heterocyclyl, -OR9, -SR9, -S(O)R9, -SO2R9, and -SO3R9; ≥1 R6 radicals = H, halogen, -CN, -NO2, hydrocarbyl, -R5, -OR13, -NR 13R14, -SR13, -S(O)R13, -S(O)2R13, -SO3R13, -S+R3R14A-, -NR13OR14, -NR13NR14R15, -OM, -SO2OM, -SO2NR13R14, -NR14C(O)R13, -C(O)OM, -S(O)NR13R14, -N+R13R14R15A-, -PR13R14, -P(O)R13R4, -P+R13R14R15A-, amino acid residue, peptide residue, polypeptide residue, and carbohydrate residue; addnl. details are given in the claims. I (X = X' = F) are

claimed to be preparable from the 4-oxo analog and diethylaminosulfur trifluoride; I (X = F; X' = H) are claimed preparable from the 4-hydroxy analog and diethylaminosulfur trifluoride. Hundreds of example prepns. of precursors to I are included, but none of I; most of the example prepns. have appeared in earlier patents (e.g. WO 98/40375). Biol. testing procedures are described but no test results are reported except for the statement that a polyethylene glycol-functionalized benzothiepine (4500 MW; a 4-hydroxy analog of I) inhibited ileal bile acid transport-mediated uptake of 14C-taurocholate in H14 cells.

- ICM C07D337-00 ICS A61K031-38 IC
- 27-21 (Heterocyclic Compounds (One Hetero Atom)) CC Section cross-reference(s): 1
- fluorinated benzothiepine prepn method inhibitor ASBT taurocholate uptake SThyperlipidemic
- Transport proteins IT

RL: BSU (Biological study, unclassified); BIOL (Biological study) (ASBT (apical sodium-dependent bile acid transporter), inhibitors; preparation of novel mono- and di-fluorinated benzothiepines as

inhibitors

of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

Bile acids IT

RL: BSU (Biological study, unclassified); BIOL (Biological study) (ASBT inhibitors; preparation of novel mono- and di-fluorinated benzothiepines as inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

Calculi, biliary IT

(dissolving agents; preparation of novel mono- and di-fluorinated benzothiepines as inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

Drug delivery systems IT

(for mono- and di-fluorinated benzothiepines as inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

Lipids, biological studies IT

RL: BSU (Biological study, unclassified); BIOL (Biological study) (hyperlipidemia; preparation of novel mono- and di-fluorinated benzothiepines as inhibitors of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

Anticholesteremic agents IT

Biological transport

Calculi, biliary

Hypercholesterolemia

(preparation of novel mono- and di-fluorinated benzothiepines as inhibitors

of apical sodium co-dependent bile acid transport (ASBT) and taurocholate uptake for treating hyperlipidemic conditions)

7440-23-5, Sodium, biological studies IT

RL: BSU (Biological study, unclassified); BIOL (Biological study) (ASBT inhibitors; preparation of novel mono- and di-fluorinated benzothiepines as inhibitors of apical sodium co-dependent bile acid

> 571-272-2528 Shears Searcher :

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transport (ASBT) and taurocholate uptake for treating hyperlipidemic
        conditions)
IT
     361373-74-2P
    RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic
    preparation); PREP (Preparation); RACT (Reactant or reagent)
        (formation and racemization; preparation of precursors of mono- and
        di-fluorinated benzothiepine inhibitors of apical sodium co-dependent
       bile acid transport (ASBT) and taurocholate uptake for treating
        hyperlipidemic conditions)
    197372-68-2P, 3-Butyl-3-ethyl-4,5-dihydroxy-5-phenyl-2,3,4,5-
IT
                                          197378-62-4P
     tetrahydrobenzothiepine-1,1-dioxide
     RL: BYP (Byproduct); PREP (Preparation)
        (preparation of precursors of mono- and di-fluorinated benzothiepine
        inhibitors of apical sodium co-dependent bile acid transport (ASBT) and
        taurocholate uptake for treating hyperlipidemic conditions)
     197373-36-7P
TT
     RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL
     (Biological study); PREP (Preparation)
        (preparation of precursors of mono- and di-fluorinated benzothiepine
        inhibitors of apical sodium co-dependent bile acid transport (ASBT) and
        taurocholate uptake for treating hyperlipidemic conditions)
     228113-60-8P
IT
     RL: PEP (Physical, engineering or chemical process); PYP (Physical
     process); SPN (Synthetic preparation); PREP (Preparation); PROC (Process)
        (preparation of precursors of mono- and di-fluorinated benzothiepine
        inhibitors of apical sodium co-dependent bile acid transport (ASBT) and
        taurocholate uptake for treating hyperlipidemic conditions)
     228113-65-3P
ΙT
     RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP
     (Preparation)
        (preparation of precursors of mono- and di-fluorinated benzothiepine
        inhibitors of apical sodium co-dependent bile acid transport (ASBT) and
        taurocholate uptake for treating hyperlipidemic conditions)
                                                        66-25-1, Hexanal
                                     55-98-1, Busulfan
     51-45-6, Histamine, reactions
TΨ
                                   100-47-0, Benzonitrile, reactions
     91-22-5, Quinoline, reactions
                                                              106-44-5,
                                   106-41-2, 4-Bromophenol
     100-66-3, Anisole, reactions
     4-Methylphenol, reactions 108-98-5, Thiophenol, reactions
                                                                   109-00-2,
     3-Hydroxypyridine 109-89-7, Diethylamine, reactions 110-18-9,
     N,N,N',N'-Tetramethylethylenediamine 110-86-1, Pyridine, reactions
     110-91-8, Morpholine, reactions 111-18-2, N,N,N',N'-Tetramethyl-1,6-
                    111-24-0, 1,5-Dibromopentane 121-44-8, Triethylamine,
     hexanediamine
                121-86-8, 2-Chloro-4-nitrophenylmethane 123-12-6,
     reactions
     N,N,N',N'-Tetraethyldiethylenetriamine 123-75-1, Pyrrolidine, reactions
     131-57-7, 2-Hydroxy-4-methoxybenzophenone 138-60-3, Chelidamic acid
     150-76-5, 4-Methoxyphenol 280-57-9, 1,4-Diazabicyclo[2.2.2]octane
     345-35-7, 2-Fluorobenzyl chloride 352-11-4, 4-Fluorobenzyl chloride
     371-41-5, 4-Fluorophenol 456-42-8, 3-Fluorobenzyl chloride
                                           504-63-2, 1,3-Propanediol
                     503-29-7, Azetidine
     Fluorobenzene
     596-75-8, Diethyl dibutylmalonate 623-25-6, \alpha,\alpha'-Dichloro-p-
              628-11-5, 3-Chloropropyl chloroformate 628-77-3,
     xylene
                         696-63-9, 4-Methoxythiophenol 705-29-3,
      1,5-Diiodopentane
     3-(Trifluoromethyl)benzyl chloride 824-98-6, 3-Methoxybenzyl chloride
     869-24-9, 2-Diethylaminoethyl chloride hydrochloride 922-63-4,
                       1633-83-6, 1,4-Butane sultone 1642-81-5,
      2-Ethylacrolein
      4-(Chloromethyl)benzoic acid 1680-78-0, 2-Ethyl-2-(hydroxymethyl)hexanal
      1801-99-6, 2-Mercaptobenzophenone 1822-51-1, 4-Picolyl chloride
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2043-61-0, Cyclohexanecarboxaldehyde
                                                           2417-72-3, Methyl
    hydrochloride
                              2516-96-3, 2-Chloro-5-nitrobenzoic acid
    4-(bromomethyl)benzoate
                                         3099-28-3, 2,6-
    2646-90-4, 2,5-Difluorobenzaldehyde
    Bis(chloromethyl)pyridine 4023-02-3, 1H-Pyrazole-1-carboxamidine
                                                         4521-31-7,
                    4509-90-4, 5-Bromovaleroyl chloride
    hydrochloride
                               4724-56-5 5\overline{4}14-19-7, Bis(2-bromoethyl) ether
    2-Mercaptobenzyl alcohol
    5437-45-6, Benzyl 2-bromoacetate 5469-66-9, 1,3-Propanediol
                                9004-74-4, MPEG 13331-27-6,
                    6290-05-7
    di-p-tosylate
                                 15014-25-2, Dibenzyl malonate
                                                                 16420-13-6,
    3-Nitrobenzeneboronic acid
                                     18982-54-2, 2-Bromobenzyl alcohol
    Dimethylthiocarbamoyl chloride
    28994-41-4, 2-Hydroxydiphenylmethane 34052-37-4, 2-Chloro-5-
                                                                   36839-55-1,
                        35730-09-7, 2,5-Difluorobenzoyl chloride
    nitrobenzophenone
                                 41602-50-0, N-(Chloroacetyl)glycine ethyl
    1,2-Bis(2-iodoethoxy)ethane
            60343-28-4, Benzyl 5-bromovalerate
                                                63024-77-1,
                                                                154932-88-4
                                                  121559-53-3
                                     99376-14-4
    3-Chloromethylbenzoyl chloride
                                              197375-48-7 197375-49-8
                                197373-14-1
                  197372-98-8
    197372-97-7
                  197378-60-2
    197378-59-9
    RL: RCT (Reactant); RACT (Reactant or reagent)
        (preparation of precursors of mono- and di-fluorinated benzothiepine
        inhibitors of apical sodium co-dependent bile acid transport (ASBT) and
        taurocholate uptake for treating hyperlipidemic conditions)
    1426-54-6P, 4-Fluoro-2-[(4-methoxyphenyl)methyl]phenol
                                                             1481-12-5P,
     4-Fluoro-2-(4'-fluorobenzyl)phenol 1515-89-5P, 3-Bromobenzyl methyl
IT
                                       16473-35-1P, 1-(Chloromethyl)-4-
                         15886-84-7P
            3670-91-5P
                             24632-01-7P, 1-(Hydroxymethyl)cyclohexanecarboxal
     (hydroxymethyl)benzene
            24765-57-9P, 2,2-Dibutyl-1,3-propanediol
                                                        70132-87-5P
                                             120936-00-7P, O-2-Benzylphenyl
     120454-34-4P, 2-Mercaptodiphenylmethane
                                                          162632-54-4P,
                                           131117-88-9P
                            120936-01-8P
     dimethylthiocarbamate
                                       163445-43-0P, 2-Mercapto-5-
     2-Mercapto-4-methoxybenzophenone
                           174747-95-6P, 1-Bromo-2-butyl-2-
     methoxybenzophenone
                                            178678-22-3P,
                            178678-21-2P
     (hydroxymethyl)hexane
     3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine
                                                         178678-23-4P,
     cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-4(5H)-one
     178678-24-5P, trans-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-4(5H)-
           178678-25-6P, cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-
     4(5H)-one-1,1-dioxide 178678-26-7P 178678-27-8P
                                                           178678-29-0P
     178678-33-6P, 3-Ethyl-5-phenyl-2,3-dihydrobenzothiepine
                                                               178678-34-7P
     178678-36-9P, cis-3-Ethyl-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-
                             178678-40-5P 178678-45-0P 178678-46-1P
              178678-37-0P
                                                                 178678-56-3P,
                                                  178678-55-2P
                                   178678-51-8P
                    178678-50-7P
     178678-49-4P
     2-[(2-Benzoylphenylthio)methyl]-2-ethylhexanal
                                                      178678-57-4P,
                                                                   178678-59-6P
                                                    178678-58-5P
     2-[(2-Benzoylphenylthio)methyl]butyraldehyde
                                                                 178678-64-3P
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     197373-47-0P
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                                                  197373-58-3P
                                   197373-57-2P
                    197373-56-1P
                    197378-07-7P, 4-Chloro-3-(4-methoxyphenylmethyl)nitrobenzen
     197373-55-0P
     197378-05-5P
                                                       197378-20-4P
                                       197378-18-0P
                        197378-16-8P
          197378-15-7P
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                     197378-44-2P
      197378-42-0P
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                                           197378-50-0P
      4-Fluoro-2-(3'-methoxybenzyl)phenol
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228113-58-4P
                                                 228113-57-3P
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                                  228113-64-2P
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   2-(Bromomethyl)-2-butylhexanal
                                       525589-60-0P
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    3-Acetoxy-2,2-dibutyl-1-propanol
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    525589-62-2P
                                                        525589-71-3P
                                         525589-69-9P
    4-Methyl-2-(4'-fluorobenzyl)phenol
   RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
    (Reactant or reagent)
       (preparation of precursors of mono- and di-fluorinated benzothiepine
       inhibitors of apical sodium co-dependent bile acid transport (ASBT) and
       taurocholate uptake for treating hyperlipidemic conditions)
    178678-28-9P, 3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine-1,1-
              178678-30-3P, cis-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-
    dioxide
                                          178678-31-4P, trans-3-Butyl-3-ethyl-
    tetrahydrobenzothiepine-1,1-dioxide
    5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide
                                                           178678-32-5P,
    3-Butyl-3-ethyl-4-hydroxy-5-cyclohexylidene-2,3,4,5-
                                                         178678-38-1P
    tetrahydrobenzothiepine-1,1-dioxide
                                          178678-35-8P
                                                                 178678-48-3P
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                                   525589-59-7P
                    361374-26-7P
    289038-50-2P
    RL: SPN (Synthetic preparation); PREP (Preparation)
        (preparation of precursors of mono- and di-fluorinated benzothiepine
       inhibitors of apical sodium co-dependent bile acid transport (ASBT) and
       taurocholate uptake for treating hyperlipidemic conditions)
    81-24-3
    RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (uptake inhibitors; preparation of novel mono- and di-fluorinated
       benzothiepines as inhibitors of apical sodium co-dependent bile acid
        transport (ASBT) and taurocholate uptake for treating hyperlipidemic
        conditions)
                               THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
REFERENCE COUNT:
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ΙT

IT

571-272-2528 Shears Searcher :

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 13 MARPAT COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

138:215326 MARPAT

TITLE:

Combined preparations, containing 1,4-benzothiepine-1,1-dioxide derivatives and other active substances

for the treatment of hyperlipidemia

INVENTOR(S):

Glombik, Heiner; Frick, Wendelin; Schaefer,

Hans-Ludwig; Kramer, Werner

PATENT ASSIGNEE(S):

Aventis Pharma Deutschland GmbH, Germany

SOURCE:

PCT Int. Appl., 40 pp.

DOCUMENT TYPE:

Patent

CODEN: PIXXD2

LANGUAGE:

German

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

$$R^4$$
 R^5
 R^2
 R^2
 R^2
 R^3
 R^3
 R^4
 R^3

The invention relates to mixts. of substances, containing 1,4-benzothiepine-1,1-dioxide derivs. of formula (I), in which the functional groups have AB the indicated meanings, their physiol. acceptable salts and physiol. functional derivs. as well as other active substances for the treatment of metabolic disorders especially hyperlipidemia. The combinations can also include antidiabetics, antiarthrytics etc. A typical capsule contains 100 mg of the drugs and 400 mg triglyceride mixture from coco fatty acids; other formulations are emulsions, tablets, dragees, and solns. Hamster that were fed with cholesterol-rich feed received orally the drug combination once daily for 10 days. Feces was analyzed for bile acids, blood lipid levels were measured and cholesterol was determined from liver.

ICM A61K031-55 IC

ICS A61K031-395; A61P003-06

1-10 (Pharmacology) CC

Section cross-reference(s): 63

benzothiepine dioxide combination drug anticholesterimics antilipemic STagent

Potassium channel ΙT

RL: BSU (Biological study, unclassified); BIOL (Biological study) (ATP-sensitive, binding drugs; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia)

Proteins IT

RL: BSU (Biological study, unclassified); BIOL (Biological study) (CRF-binding protein, antagonists; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia)

Lipoprotein receptors IT

RL: BSU (Biological study, unclassified); BIOL (Biological study) (LDL, inducers; combined prepns., containing

1,4-benzothiepine-1,1-dioxide

derivs. and other active substances for treatment of hyperlipidemia)

Lipoproteins IT

RL: BSU (Biological study, unclassified); BIOL (Biological study) (Lp(a), antagonists; combined prepns., containing 1,4-benzothiepine-1,1dioxide derivs. and other active substances for treatment of hyperlipidemia)

Proteins IT

RL: BSU (Biological study, unclassified); BIOL (Biological study)

571-272-2528 Shears Searcher :

(MTP (microsomal triglyceride-exchanging protein), inhibitors; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Retinoid X receptors RL: BSU (Biological study, unclassified); BIOL (Biological study) ידיד (RXR, modulators; combined prepns., containing 1,4-benzothiepine-1,1dioxide derivs. and other active substances for treatment of hyperlipidemia) Peroxisome proliferator-activated receptors ΙT RL: BSU (Biological study, unclassified); BIOL (Biological study) $(a/\gamma$, agonists; combined prepns., containing 1,4-benzothiepine-1,1dioxide derivs. and other active substances for treatment of hyperlipidemia) Bile acids ITRL: BSU (Biological study, unclassified); BIOL (Biological study) (adsorbers; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Tumor necrosis factors ITRL: BSU (Biological study, unclassified); BIOL (Biological study) (agonist; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Drug delivery systems ΙT (capsules; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) IT Proteins RL: BSU (Biological study, unclassified); BIOL (Biological study) (cholesterol ester-exchanging, inhibitors; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) 5-HT agonists IT Antiarthritics Anticholesteremic agents Antidiabetic agents Antioxidants Hypercholesterolemia Hypolipemic agents (combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Sulfonylureas IT RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Drug delivery systems (dragees; combined prepns., containing 1,4-benzothiepine-1,1-dioxide IT derivs. and other active substances for treatment of hyperlipidemia) Drug delivery systems (emulsions; combined prepns., containing 1,4-benzothiepine-1,1-dioxide IT derivs. and other active substances for treatment of hyperlipidemia) Neurotransmitter agonists ΙT (histaminic H3, agonists; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Lipids, biological studies ΙT RL: BSU (Biological study, unclassified); BIOL (Biological study)

```
(hyperlipidemia; combined prepns., containing
1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
     Pituitary hormone receptors
IΤ
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (melanocortin receptor 4, MT-4, agonists; combined prepns., containing
        1,4-benzothiepine-1,1-dioxide derivs. and other active substances for
        treatment of hyperlipidemia)
     Peroxisome proliferator-activated receptors
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (modulators; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
IT
     Receptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (peptide, cocaine and amphetamine-regulated transcript peptide,
        agonists; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
     Bile acids
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (resorption inhibitors; combined prepns., containing
1,4-benzothiepine-1,1-
        dioxide derivs. and other active substances for treatment of
        hyperlipidemia)
     Drug delivery systems
        (tablets; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
     Peroxisome proliferator-activated receptors
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (\alpha, agonists; combined prepns., containing 1,4-benzothiepine-1,1-
        dioxide derivs. and other active substances for treatment of
        hyperlipidemia)
     Thyroid hormone receptors
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (β, agonists; combined prepns., containing 1,4-benzothiepine-1,1-
        dioxide derivs. and other active substances for treatment of
        hyperlipidemia)
     Peroxisome proliferator-activated receptors
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (\gamma, agonists; combined prepns., containing 1,4-benzothiepine-1,1-
        dioxide derivs. and other active substances for treatment of
        hyperlipidemia)
                      245359-74-4, Orexin
     9015-71-8, CRF
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (agonist; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
     9002-79-3, Melanocyte-stimulating hormone 9011-97-6, Cholecystokinin
IT
                                             82785-45-3, Neuropeptide Y
                        31362-50-2, Bombesin
     24305-27-9, TRH
     193830-48-7, Urocortin 202347-31-7, Leptin E
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (agonists; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
     119418-04-1, Galanin
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (antagonists; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
     57-88-5, Cholesterol, biological studies
IT
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RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and
         other active substances for treatment of hyperlipidemia)
      56-03-1, Biguanide 300-62-9, Amphetamine 943-45-3, Fibric acid
ΙT
                                              9000-40-2, Carob gum
      2295-31-0, Glitazone 5395-30-2
                         9004-10-8, Insulin, biological studies 9034-39-3,
      Growth hormone
      Growth hormone releasing hormone 11041-12-6, Cholestyramine
      25614-03-3, Bromocriptine 25812-30-0, Gemfibrozil 49642-07-1, Statine
      50925-79-6, Cholestipol 54870-28-9, Meglitinide 96829-58-2, Orlistat
                                                               150332-35-7, Pamaqueside
      99759-19-0, Tiqueside 129024-87-9, Doprexin
      163222-33-1, Ezetimibe 252047-40-8
      RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
      (Biological study); USES (Uses)
          (combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and
         other active substances for treatment of hyperlipidemia)
      9000-92-4, Amylase 9027-63-8, ACAT
IT
      RL: BSU (Biological study, unclassified); BIOL (Biological study)
          (inhibitor; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
          derivs. and other active substances for treatment of hyperlipidemia)
      50-67-9, biological studies 9001-42-7, \alpha-Glucosidase 9001-62-1,
IT
      Lipase 9004-02-8, Lipoprotein-Lipase 9027-95-6, ATP-Citrate-Lyase
      9028-35-7, HMG-CoA-Reductase 9077-14-9, Squalene synthase
      RL: BSU (Biological study, unclassified); BIOL (Biological study)
          (inhibitors; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
          derivs. and other active substances for treatment of hyperlipidemia)
                                     THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
REFERENCE COUNT:
                                      RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
L19 ANSWER 5 OF 13 MARPAT COPYRIGHT 2004 ACS on STN
                               138:215324 MARPAT
ACCESSION NUMBER:
                              Combined preparations, containing 1,4-benzothiepine-
TITLE:
                               1,1-dioxide derivatives and other active substances
                               for the treatment of hyperlipidemia
                               Glombik, Heiner; Frick, Wendelin; Schaefer,
INVENTOR(S):
                               Hans-Ludwig; Kramer, Werner
                              Aventis Pharma Deutschland G.m.b.H., Germany
PATENT ASSIGNEE(S):
                               Ger. Offen., 10 pp.
SOURCE:
                               CODEN: GWXXBX
                               Patent
DOCUMENT TYPE:
                               German
LANGUAGE:
FAMILY ACC. NUM. COUNT:
PATENT INFORMATION:
                                                   APPLICATION NO. DATE
                         KIND DATE
       PATENT NO.
                                                    -----
                                                   DE 2001-10140169 20010822
      DE 10140169
                            A1
                                   20030306
                                                   WO 2002-EP8908 20020809
           2003018024 Al 20030306 WO 2002-EP8908 20020809

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PI, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
                           A1 20030306
      WO 2003018024
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NE, SN, TD, TG EP 2002-796213 20020809 20040609 EP 1425018 Α1 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK 20020822 US 2002-225841 20030821 US 2003158119 A120031103 US 2003-699967 20040520 US 2004097424 Α1 DE 2001-10140169 20010822 PRIORITY APPLN. INFO.: DE 2001-10142456 20010831 20020809 WO 2002-EP8908 20020822 US 2002-225841

GΙ

The invention relates to mixts. of substances, containing 1,4-benzothiepine-AΒ 1,1-dioxide derivs. of formula (I), in which the functional groups have the indicated meanings, their physiol. acceptable salts and physiol. functional derivs. as well as other active substances for the treatment of metabolic disorders especially hyperlipidemia. The combination can also include

antidiabetics, antiarthrytics etc. A typical capsule contains 100 mg of the drugs and 400 mg triglyceride mixture form coco fatty acids; other formulations are emulsions, tablets, dragees, and solns. The inhibition of sodium-dependent uptake of [3H]-taurocholate (TC) into brush border membrane vesicles was measured.

ICM A61K038-07 IC

ICS A61K038-06; A61K038-05; A61K031-7008

Ι

1-10 (Pharmacology) CC

Section cross-reference(s): 63

benzothiepine dioxide combination drug anticholesterimics antilipemic STagent

Potassium channel ΙT

RL: BSU (Biological study, unclassified); BIOL (Biological study) (ATP-sensitive, binding drugs; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia)

ΙT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study) (CRF-binding protein, antagonists; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia)

> 571-272-2528 Shears Searcher :

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Lipoprotein receptors
ΙT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (LDL, inducers; combined prepns., containing
1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
     Lipoproteins
TΤ
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (Lp(a), antagonists; combined prepns., containing 1,4-benzothiepine-1,1-
        dioxide derivs. and other active substances for treatment of
        hyperlipidemia)
     Proteins
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (MTP (microsomal triglyceride-exchanging protein), inhibitors; combined
        prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other
active
        substances for treatment of hyperlipidemia)
     Retinoid X receptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
IT
        (RXR, modulators; combined prepns., containing 1,4-benzothiepine-1,1-
        dioxide derivs. and other active substances for treatment of
        hyperlipidemia)
     Peroxisome proliferator-activated receptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
IT
         (a/\gamma \text{ agonists}; \text{ combined prepns., containing } 1,4-benzothiepine-1,1-
        dioxide derivs. and other active substances for treatment of
        hyperlipidemia)
     Tumor necrosis factors
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (agonist; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
      Drug delivery systems
 ΙT
         (capsules; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
         derivs. and other active substances for treatment of hyperlipidemia)
      Proteins
 IT
      RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (cholesterol ester-exchanging, inhibitors; combined prepns., containing
         1,4-benzothiepine-1,1-dioxide derivs. and other active substances for
         treatment of hyperlipidemia)
 TΨ
      5-HT agonists
      Antiarthritics
      Anticholesteremic agents
      Antidiabetic agents
      Antioxidants
      Hypercholesterolemia
      Hypolipemic agents
          (combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and
         other active substances for treatment of hyperlipidemia)
      Sulfonylureas
 IT
      RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
       (Biological study); USES (Uses)
          (combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and
          other active substances for treatment of hyperlipidemia)
      Drug delivery systems
          (dragees; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
 ΤТ
          derivs. and other active substances for treatment of hyperlipidemia)
      Drug delivery systems
 IΤ
```

(emulsions; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Neurotransmitter agonists (histaminic H3, agonists; combined prepns., containing 1,4-benzothiepine-ΙT 1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Lipids, biological studies ΙT RL: BSU (Biological study, unclassified); BIOL (Biological study) (hyperlipidemia; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Pituitary hormone receptors RL: BSU (Biological study, unclassified); BIOL (Biological study) (melanocortin receptor 4, MT-4, agonists; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Peroxisome proliferator-activated receptors TТ RL: BSU (Biological study, unclassified); BIOL (Biological study) (modulators; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Receptors ΙT RL: BSU (Biological study, unclassified); BIOL (Biological study) (peptide, cocaine and amphetamine-regulated transcript peptide, agonists; combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Bile acids ITRL: BSU (Biological study, unclassified); BIOL (Biological study) (polymeric, adsorbers; combined prepns., containing 1,4-benzothiepine-1,1dioxide derivs. and other active substances for treatment of hyperlipidemia) Bile acids IT RL: BSU (Biological study, unclassified); BIOL (Biological study) (resorption inhibitors; combined prepns., containing 1,4-benzothiepine-1,1dioxide derivs. and other active substances for treatment of hyperlipidemia) Transport proteins TΤ RL: BSU (Biological study, unclassified); BIOL (Biological study) (sodium dependent taurocholate, inhibition of; combined prepris., containing 1,4-benzothiepine-1,1-dioxide derivs. and other active substances for treatment of hyperlipidemia) Drug delivery systems (tablets; combined prepns., containing 1,4-benzothiepine-1,1-dioxide ITderivs. and other active substances for treatment of hyperlipidemia) Peroxisome proliferator-activated receptors TΤ RL: BSU (Biological study, unclassified); BIOL (Biological study) $(\alpha$, agonists; combined prepns., containing 1,4-benzothiepine-1,1dioxide derivs. and other active substances for treatment of hyperlipidemia) Thyroid hormone receptors TΤ RL: BSU (Biological study, unclassified); BIOL (Biological study) $(\beta$, agonists; combined prepns., containing 1,4-benzothiepine-1,1dioxide derivs. and other active substances for treatment of hyperlipidemia)

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Peroxisome proliferator-activated receptors
IT
    RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (γ, agonists; combined prepns., containing 1,4-benzothiepine-1,1-
       dioxide derivs. and other active substances for treatment of
        hyperlipidemia)
                      245359-74-4, Orexin
     9015-71-8, CRF
IT
    RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (agonist; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
                                                9011-97-6, Cholecystokinin
     9002-79-3, Melanocyte-stimulating hormone
IT
                                             82785-45-3, Neuropeptide Y
                       31362-50-2, Bombesin
     24305-27-9, TRH
                          193830-48-7, Urocortin
     169494-85-3, Leptin
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (agonists; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
     119418-04-1, Galanin
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (antagonists; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
     57-88-5, Cholesterol, biological studies
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and
        other active substances for treatment of hyperlipidemia)
                                                 943-45-3, Fibric acid
     56-03-1, Biguanide 300-62-9, Amphetamine
TΨ
                                                  9002-72-6, Growth hormone
     2295-31-0, 2,4-Thiazolidinedione
                                       5395-30-2
                                              9034-39-3, Growth hormone
     9004-10-8, Insulin, biological studies
                                                      25614-03-3, Bromocriptine
     releasing hormone 11041-12-6, Cholestyramine
                                                    50925-79-6, Cholestipol
                              49642-07-1, Statine
     25812-30-0, Gemfibrozil
                                                    99759-19-0, Tiqueside
     54870-28-9, Meglitinide 96829-58-2, Orlistat
                                                        163222-33-1, Ezetimibe
                            150332-35-7, Pamaqueside
     129024-87-9, Doprexin
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (combined prepns., containing 1,4-benzothiepine-1,1-dioxide derivs. and
        other active substances for treatment of hyperlipidemia)
     9000-92-4, Amylase 9027-63-8, ACAT
ΤТ
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (inhibitor; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
     50-67-9, biological studies 9001-42-7, \alpha-Glucosidase
                                                              9001-62-1,
IT
              9004-02-8, Lipoprotein-Lipase 9027-95-6, ATP-Citrate-Lyase
     9028-35-7, HMG-CoA-Reductase 9077-14-9, Squalene synthase
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (inhibitors; combined prepns., containing 1,4-benzothiepine-1,1-dioxide
        derivs. and other active substances for treatment of hyperlipidemia)
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (sodium dependent uptake, inhibition of; combined prepns., containing
         1,4-benzothiepine-1,1-dioxide derivs. and other active substances for
         treatment of hyperlipidemia)
L19 ANSWER 6 OF 13 MARPAT COPYRIGHT 2004 ACS on STN
                          137:63115 MARPAT
 ACCESSION NUMBER:
                          Preparation of diphenylazetidinone derivatives as
 TITLE:
                          hypolipidemic agents
                          Glombik, Heiner; Kramer, Werner; Flohr, Stefanie;
 INVENTOR(S):
                          Frick, Wendelin; Heuer, Hubert; Jaehne, Gerhard;
```

Lindenschmidt, Andreas; Schaefer, Hans-Ludwig

PATENT ASSIGNEE(S): SOURCE:

Aventis Pharma Deutschland GmbH, Germany

PCT Int. Appl., 67 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND DATE	APPLICATION NO. DATE
WO 2002050068 W: AE, AG, CO, CR, GM, HR, LS, LT, PL, PT, UG, UZ, RW: GH, GM, CY, DE, BF, BJ, DE 10064402 DE 10154520 AU 2002019173 EE 200300237 EP 1345932 R: AT, BE, IE, SI, BR 2001016482 JP 2004516293 US 2002128252 US 6498156	A1 20020627 AL, AM, AT, AU, AZ, CU, CZ, DE, DK, DM, HU, ID, IL, IN, IS, LU, LV, MA, MD, MG, RO, RU, SD, SE, SG, VN, YU, ZA, ZM, ZW, KE, LS, MW, MZ, SD, DK, ES, FI, FR, GB, CF, CG, CI, CM, A1 20020627 A1 20031002 A5 20020701 A 20030815 A1 20030924 CH, DE, DK, ES, FR, LT, LV, FI, RO, MK, A 20040203 T2 20040603 A1 20020912 B2 20021224 A 20030814	WO 2001-EP14532 20011211 , BA, BB, BG, BR, BY, BZ, CA, CH, CN, DZ, EC, EE, ES, FI, GB, GD, GE, GH, JP, KE, KG, KP, KR, KZ, LC, LK, LR, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, GR, IE, IT, LU, MC, NL, PT, SE, TR, GN, GQ, GW, ML, MR, NE, SN, TD, TG DE 2000-10064402 20001221 DE 2001-10154520 20011107 AU 2002-19173 20011211 EE 2003-237 20011211 EE 2003-237 20011211 GB, GR, IT, LI, LU, NL, SE, MC, PT, CY, AL, TR BR 2001-16482 20011211 JP 2002-551564 20011211
GI		WO 2001-EP14532 20011211

- * STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY AVAILABLE VIA OFFLINE PRINT *
- The compds. are suited for use e.g. as hypolipidemic drugs. The invention AΒ discloses preparation of diphenylazetidinone derivs. such as I [R1, R2, R3, R4,
 - R5, R6 = C0-C30-alkylene-L {optionally containing O, CO, CH:CH, C.tplbond.C, N(alkyl), N(alkylphenyl), NH), H, F, Cl, Br, I, CF3, NO2, CN, CO2H, CO2(alkyl), CONH2, CONH(alkyl), CON(alkyl)2, alkyl, alkenyl, alkynyl, O-alkyl, SO2NH2, SO2NH(alkyl) SO2N(alkyl)2, S-(alkyl), SO(alkyl), (un) substituted S(CH2) nPh, SO(CH2) nPh, SO2(alkyl), SO2(CH2) nPh, NH2, NH(alkyl), N(alkyl)2, NH(acyl), (un)substituted Ph, O(CH2)nPh; n = 0-6; L = II; R7, R9, R10 = Me, Et, Pr, butyl; R8 = H, OH, NH2, NH(alkyl)], and their physiol. acceptable salts, for their use as hypolipidemic agents. Thus, 1,2-diphenylazetidinone derivative III trifluoroacetate (IV) was prepared via a multistep synthetic sequence starting from

```
7-[3-(3-butyl-7-dimethylamino-3-ethyl-4-hydroxy-1,1-dioxo-2,3,4,5-
     tetrahydro-1H-benzo[b]thiepin-5-yl)-phenylcarbamoyl]-heptanoic acid and
     4-(4-aminomethylphenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-
     hydroxyphenyl]-azetidin-2-one. Azetidinone IV was tested for its
     cholesterol lowering ability [ED50 = 0.01 mg/mouse].
     ICM C07D409-12
     ICS A61K031-397; A61P009-00
     26-5 (Biomolecules and Their Synthetic Analogs)
CC
     Section cross-reference(s): 1, 63
     azetidinone diphenyl deriv prepn hypolipidemic; diphenylazetidinone prepn
ST
     hypolipidemic
IT
     Antiarteriosclerotics
        (antiatherosclerotics; preparation of diphenylazetidinone derivs. as
        hypolipidemics)
     Lipids, biological studies
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (hyperlipidemia, medicaments; preparation of diphenylazetidinone derivs.
as
        hypolipidemics)
IT
     Diabetes mellitus
        (insulin-resistant, medicaments; preparation of diphenylazetidinone
derivs.
        as hypolipidemics)
    Arteriosclerosis
IT
        (medicaments; preparation of diphenylazetidinone derivs. as
hypolipidemics)
     Lipids, biological studies
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (metabolic disorders, medicaments; preparation of diphenylazetidinone
        derivs. as hypolipidemics)
     Anticholesteremic agents
TT
     Antidiabetic agents
     Human
     Hypolipemic agents
        (preparation of diphenylazetidinone derivs. as hypolipidemics)
     Peroxisome proliferator-activated receptors
IT
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (\gamma, agonist; preparation of diphenylazetidinone derivs. as
        hypolipidemics)
     57-88-5, Cholest-5-en-3-ol (3\beta)-, biological studies
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     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (medicaments; preparation of diphenylazetidinone derivs. as
hypolipidemics)
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     RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
        (preparation of diphenylazetidinone derivs. as hypolipidemics)
     76-05-1, Trifluoroacetic acid, reactions 112-60-7, Tetraethylene glycol
TΤ
     124-04-9, Hexanedioic acid, reactions 1117-97-1, O,N-
                             1501-05-9 1663-39-4, tert-Butyl acrylate
     Dimethylhydroxylamine
     7480-32-2, 4-Phenyl-oxazolidin-2-one 20256-89-7 23243-68-7
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        (preparation of diphenylazetidinone derivs. as hypolipidemics)
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         (preparation of diphenylazetidinone derivs. as hypolipidemics)
                                THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
REFERENCE COUNT:
                         5
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
L19 ANSWER 7 OF 13 MARPAT COPYRIGHT 2004 ACS on STN
                          135:257255 MARPAT
ACCESSION NUMBER:
                         preparation of chiral azaazoniabicyclooctylmethylbenzy
TITLE:
                         loxyphenyltetrahydrobenzothiepines by amination of the
                         corresponding benzyl alcohols.
                         Babiak, Kevin A.; Carpenter, Andrew; Chou, Shine;
INVENTOR(S):
                         Colson, Pierre-Jean; Farid, Payman; Hett, Robert;
                         Huber, Chrisistian H.; Koeller, Kevin J.; Lawson, Jon
                         P.; Li, James; Mar, Eduardo K.; Miller, Lawrence M.;
                         Orlovski, Vladislav; Peterson, James C.; Pozzo, Mark
                          J.; Przybyla, Claire A.; Tremont, Samuel J.; Trivedi,
                          Jay S.; Wagner, Grace M.; Weisenburger, Gerald A.;
                         Zhi, Benxin
                         Pharmacia Corporation, USA
PATENT ASSIGNEE(S):
                         PCT Int. Appl., 258 pp.
SOURCE:
                         CODEN: PIXXD2
DOCUMENT TYPE:
                         Patent
LANGUAGE:
                         English
FAMILY ACC. NUM. COUNT:
PATENT INFORMATION:
     PATENT NO.
                                          APPLICATION NO. DATE
                     KIND DATE
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     _____ ___
                            _____
                                          WO 2001-US7421 20010308
                             20010920
     WO 2001068637
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             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
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             AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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JP 2001-567729

20010308

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR T2 20030930

JP 2003528830

US 2002-204826 20021223 A1 20031225 US 2003236406 US 2003-419266 20030421 US 2004082647 A120040429 20030703 US 2003-611942 US 2004110761 A1 20040610 20000310 US 2000-188361P PRIORITY APPLN. INFO .: US 2000-188378P 20000310 20010308 US 2001-802279 20010308 US 2001-802313 20010308 WO 2001-US7421

OTHER SOURCE(S):

CASREACT 135:257255

GI

Title compds. [I; Q = (X-)R3R4R5N; R1, R2 = hydrocarbyl; R3-R5 = H, (O-, S-, or N-interrupted) hydrocarbyl; ≥2 of R3-R5 form a cyclic structure; R9 = H, hydrocarbyl, hydroxyalkyl, OR3, NR3R4, N+R3R4R5 A-, etc.; A- = pharmaceutically acceptable cation; X- = leaving group; n = O-4], were prepared by derivatization of I (Q = OH; other variables as above) to give I (Q = X; other variables as above) and treatment of the latter with NR3R4R5. Thus, (4R,5R)-3,3-dibutyl-7-dimethylamino-1,1-dioxido-4-hydroxy-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzothiepine (preparation given) in dimethylacetamide was treated with NaOH and then with 1-chloromethyl-4-hydroxymethylbenzene (preparation given) followed by

heating

at 50° for 4 h. The crude product was stirred with SOC12 in PhMe and the chloromethyl product solution was treated with MeCOEt, H2O, and diazabicyclo[2.2.2]octane followed by reflux to give (4R,5R)-1-[[4-[4-(3,3-dibutyl-7-dimethylamino-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl)phenoxy]methyl]phenyl]methyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride.

IC ICM C07D337-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 45

Ι

azaazoniabicyclooctylmethylbenzyloxyphenyltetrahydrobenzothiepine prepn;
benzothiepine dioxide dimethylamino tetrahydro
azaazoniabicyclooctylmethylbenzyloxyphenyl prepn;
hydroxymethylbenzyloxyphenyltetrahydrobenzothiepine amination DABCO

IT Amination

(preparation of chiral

azaazoniabicyclooctylmethylbenzyloxyphenyltetrahydrob

enzothiepines by amination of the corresponding benzyl alcs.)

IT 228113-66-4P 228113-67-5P

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RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP
     (Preparation)
        (preparation of chiral
{\tt azaazoniabic} \bar{\tt yclooctylmethylbenzyloxyphenyltetrahydrob}
        enzothiepines by amination of the corresponding benzyl alcs.)
     228113-64-2P
IT
    RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic
    preparation); PREP (Preparation); RACT (Reactant or reagent)
        (preparation of chiral
azaazoniabicyclooctylmethylbenzyloxyphenyltetrahydrob
        enzothiepines by amination of the corresponding benzyl alcs.)
                                   122-51-0, Triethylorthoformate
                                                                      280-57-9,
     100-66-3, Anisole, reactions
IT
             507-09-5, Thiolacetic acid, reactions 596-75-8, Diethyl
                       598-32-3, 2-Hydroxy-3-butene 616-25-1, 1-Penten-3-ol
     dibutylmalonate
                1070-66-2, 2-Butylacrolein 1642-81-5, 4-Chloromethylbenzoic
     657-84-1
            2463-63-0, Butylacrolein 2516-96-3, 2-Chloro-5-nitrobenzoic acid
                                                               10387-40-3,
     5138-90-9, Benzenesulfonic acid, 4-chloro-, sodium salt
     Potassium thioacetate 56102-14-8 361374-10-9
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     361374-17-6
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (preparation of chiral
{\tt azaazoniabicyclooctylmethylbenzyloxyphenyltetrahydrob}
        enzothiepines by amination of the corresponding benzyl alcs.)
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     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
         (preparation of chiral
{\tt azaazoniabicyclooctylmethylbenzyloxyphenyltetrahydrob}
        enzothiepines by amination of the corresponding benzyl alcs.)
L19 ANSWER 8 OF 13 MARPAT COPYRIGHT 2004 ACS on STN
                          133:193089 MARPAT
ACCESSION NUMBER:
                          Preparation of substituted 5-aryl-benzothiepines as
TITLE:
                          ileal bile acid transport and taurocholate uptake
                          Lee, Len F.; Banerjee, Shyamal C.; Huang, Horng-chih;
INVENTOR(S):
                          Li, Jinglin J.; Miller, Raymond E.; Reitz, David B.;
                          Tremont, Samuel J.
                          G.D. Searle and Co., USA
PATENT ASSIGNEE(S):
                          U.S., 191 pp., Cont.-in-part of U.S. Ser. No.
SOURCE:
                          109,551.
                          CODEN: USXXAM
                          Patent
DOCUMENT TYPE:
                          English
 LANGUAGE:
 FAMILY ACC. NUM. COUNT:
 PATENT INFORMATION:
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PRIORITY APPLN. INFO.:
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                                           WO 1999-US12828 19990629
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US 1999-443403 19991119 US 2000-676466 20000929 US 2000-581897 20001002

GΙ

$$(R?) q \xrightarrow{(O) n} R^7$$

$$R^8$$

$$R^1$$

$$R^2$$

$$R^3$$

$$R^3$$

$$R^3$$

$$R^4$$

The title compds. (I) [wherein q = 1-4; n = 2; R1 and R2 = independently H AB or (un) substituted (halo) alkyl, alkenyl, alkynyl, alkylaryl, arylalkyl, alkoxy(alkyl), dialkylamino, alkylthio, (polyalkyl)aryl, or cycloalkyl; or R1 and R2 taken together with the atoms to which they are attached = cycloalkyl; R3 and R4 = independently H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, OR9, NR9R10, SR9, S(O)R9, SO2R9, or SO3R9; R9 and R10 = independently H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), acyl, heterocyclyl, or ammoniumalkyl; or R3 and R4 together = :0, :NOR11, :S, :NNR11R12, :NR9, or :CR11R12; R11 and R12 = independently H, (cyclo)alkyl, alkenyl, alkynyl, aryl(alkyl), heterocyclyl, carboxylalkyl, carboalkoxyalkyl, cyanoalkyl, OR9, NR9R10, SR9, S(0)R9, SO2R9, SO3R9, CO2R9, CN, halo, oxo, or CONR9R10; R5 = substituted aryl; R6 = H; R7 and R8 = independently H or alkyl; Rx = independently H or (un) substituted (cyclo)alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl(alkyl), halo(alkyl), (quaternary) heterocyclyl, (quaternary) heteroaryl, polyether, alkoxy, amino, alkylthio, NO2, carboxy, carbamido, etc.] where prepared for the prophylaxis and treatment of hyperlipidemic conditions, such as those associated with atherosclerosis or hypercholesterolemia.

Thus,

KOBu-t was added to a solution of 2-((2-benzyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (preparation given) and dry THF cooled to -1.6°C to give, after workup, II and III (96% combined yield). The isomers were separated upon recrystn. II inhibited

IBAT-mediated uptake of [14C]-taurocholate in H14 cells with an IC50 of 0.1 μM and reduced serum cholesterol from 143 mg (7%) to 126 mg (2%) compared to control in cholesterol-fed hamsters in a 14-day test. In vitro taurocholate uptake assay data are included for nearly 600 compds. of the invention.

Searcher: Shears 571-272-2528

```
C07D337-00; C07D487-00; A61K031-38; A61K031-495
TC
NCL
     549009000
     27-21 (Heterocyclic Compounds (One Hetero Atom))
CC
     Section cross-reference(s): 1
     arylbenzothiepine prepn ileal bile acid transport inhibitor; benzothiepine
ST
     prepn taurocholate uptake inhibitor; hypolipidemic antiatherosclerotic
     hypocholesterolemic arylbenzothiepine prepn
IT
     Antiarteriosclerotics
        (antiatherosclerotics; preparation of substituted 5-aryl-benzothiepines
by
        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
     Bile acids
IT
     RL: BPR (Biological process); BSU (Biological study, unclassified); MSC
     (Miscellaneous); BIOL (Biological study); PROC (Process)
        (inhibition of ileal; preparation of substituted 5-aryl-benzothiepines by
        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
     Anticholesteremic agents
ΙT
     Hypolipemic agents
        (preparation of substituted 5-aryl-benzothiepines by cyclization of
        2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile
        acid transport and taurocholate uptake inhibitors)
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     study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT
     (Reactant or reagent); USES (Uses)
        (hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by
        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
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     study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); USES (Uses)
        (hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by
        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
   (hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by
   cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
   ileal bile acid transport and taurocholate uptake inhibitors)
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study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
   (hypolipemic agent; preparation of substituted 5-aryl-benzothiepines by
   cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
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     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (intermediate; preparation of substituted 5-aryl-benzothiepines by
        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
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     study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); USES (Uses)
        (preparation of substituted 5-aryl-benzothiepines by cyclization of
        2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile
        acid transport and taurocholate uptake inhibitors)
                                             57-88-5, Cholesterol, biological
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               81-24-3
     RL: BPR (Biological process); BSU (Biological study, unclassified); MSC
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        (preparation of substituted 5-aryl-benzothiepines by cyclization of
        2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile
        acid transport and taurocholate uptake inhibitors)
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        (preparation of substituted 5-aryl-benzothiepines by cyclization of
        2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile
        acid transport and taurocholate uptake inhibitors)
     28994-41-4, 2-Hydroxydiphenylmethane
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     RL: RCT (Reactant); RACT (Reactant or reagent)
        (preparation of substituted 5-aryl-benzothiepines by cyclization of
        2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as ileal bile
        acid transport and taurocholate uptake inhibitors)
     51-45-6, Histamine, reactions 55-98-1, Busulfan
                                                       68-12-2, reactions
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                         106-41-2, 4-Bromophenol 110-86-1, Pyridine,
     100-66-3, reactions
               110-91-8, Morpholine, reactions 111-24-0, 1,5-Dibromopentane
     reactions
     111-96-6, 2-Methoxyethyl ether 123-12-6, N,N,N',N'-Tetraethyl
                        123-75-1, Pyrrolidine, reactions 131-57-7,
     diethylenetriamine
     2-Hydroxy-4-methoxybenzophenone 138-60-3, Chelidamic acid
                                                                  150-19-6,
                     150-76-5, 4-Methoxyphenol 280-57-9,
     3-Methoxyphenol
     1,4-Diazabicyclo[2.2.2]octane
                                   352-11-4, 4-Fluorobenzyl chloride
                                                      504-63-2, 1,3-Propanediol
     371-41-5, 4-Fluorophenol
                              503-29-7, Azetidine
               623-25-6, \alpha, \alpha'-Dichloro-p-xylene
                                                  628-11-5,
                                  628-77-3, 1,5-Diiodopentane
     3-Chloropropyl chloroformate
                          705-29-3, 3-(Trifluoromethyl)benzyl chloride
     4-Methoxythiophenol
     824-98-6, 3-Methoxybenzyl chloride 869-24-9, 2-Diethylaminoethyl
                             922-63-4, 2-Ethylacrolein
     chloride hydrochloride
                                                         1120-71-4,
                          1633-83-6, 1,4-Butane sultone
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     1,3-Propane sultone
     2-Ethyl-2-(hydroxymethyl)hexanal 1801-99-6, 2-Mercaptobenzophenone
     1822-51-1, 4-Picolyl chloride hydrochloride 2043-61-0,
     Cyclohexanecarboxaldehyde 2417-72-3, Methyl 4-(bromomethyl)benzoate
     2516-96-3, 2-Chloro-5-nitrobenzoic acid 2646-90-4, 2,5-
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Difluorobenzaldehyde
                           3099-28-3, 2,6-Bis(chloromethyl)pyridine
     4509-90-4, 5-Bromovaleroyl chloride 4521-31-7 4724-56-5
                                                                5414-19-7,
     Bis(2-bromoethyl)ether 5469-66-9, 1,3-Propanediol di-p-tosylate
     6290-05-7 7136-51-8, N,N,N',N'-Tetraethyl 1,6-hexanediamine
     13331-27-6, 3-Nitrobenzeneboronic acid
                                            15014-25-2, Dibenzyl malonate
     15852-73-0 34052-37-4, 2-Chloro-5-nitrobenzophenone
                                                           36839-55-1,
     1,2-Bis(2-iodoethoxy)ethane 41602-50-0, N-(Chloroacetyl)glycine ethyl
            60343-28-4, Benzyl 5-bromovalerate 63024-77-1,
     3-Chloromethylbenzoyl chloride 121559-53-3 128114-91-0
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     RL: RCT (Reactant); RACT (Reactant or reagent)
        (starting material; preparation of substituted 5-aryl-benzothiepines by
        cyclization of 2-((2-benzyl- and 2-benzoylphenylthio)methyl)alkanals as
        ileal bile acid transport and taurocholate uptake inhibitors)
                              THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS
REFERENCE COUNT:
                        56
                              RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
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ACCESSION NUMBER:

132:35625 MARPAT

TITLE:

Amino acid containing benzo[b]thiepine 1,1-dioxide

derivatives as hypolipemic agents

INVENTOR(S):

Frick, Wendelin; Enhsen, Alfons; Glombik, Heiner;

Heuer, Hubert

PATENT ASSIGNEE(S):

Hoechst Marion Roussel Deutschland G.m.b.H., Germany

SOURCE:

PCT Int. Appl., 28 pp. CODEN: PIXXD2

Patent German

DOCUMENT TYPE: LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

	rent -				ND	DATE				PPLI			0.	DATE				
	9964	410		Α	- - 1	1999	1216		W	0 19	99-E	P370	1	1999	0528			
	W:	AE,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BY,	CA,	CH,	CN,	CU,	CZ,	
		DE,	DK,	EE,	ES,	FI,	GB,	GD,	GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	
		JP,	KE,	KG,	KP,	KR,	ΚZ,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	MD,	MG,	MK,	
		MN,	MW,	MX,	NO,	NZ,	PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	
		TM,	TR,	TT,	UA,	UG,	US,	UZ,	VN,	YU,	ZA,	ZW,	AM,	ΑZ,	BY,	KG,	KZ,	
			RU,															
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													SE,	BF,	ВJ,	CF,	CG,	
		CI,	CM,	GΑ,	GN,	GW,	ML,	MR,	NE,	SN,	TD,	ΤG						
	1982								D:	E 19:	98-1	9825	804	1998	0610			
DE	1982	5804		C.	2	2000	0824											
	2334									A 19	99-2	3347	75	1999	0528			
	9945								A	U 19	99-4	5019		1999	0528			
Ν	7532	75		В	2	2002	1010								0500			
	1086								Ε	P 19	99-9	2778	4	1999	0528			
EΡ	1086					2002									a =	- m	T m	
		AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	IT,	LI,	LU,	NL,	SE,	PT,	IE,	F.T
	9912													1999				
TR	2000	0363	4	T	2	2001	0621		T	R 20	00-2	0000	3634	1999	0528			
JP	2002	5174	91	Т	2	2002	0618		J	P 20	00-5	5341	9	1999	0528			
ΑT	2277	15		E		2002	1115		A	T 19	99-9	2778	4	1999	0528			
ES	2182	535		Т	3	2003	0301		E	S 19	99-9	2778	4	1999	0528			

20030331

PT 1086092

PT 1999-927784

19990528

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RU 2001-101491
                                                            19990528
     RU 2215001
                       C2
                            20031027
                                           TR 2000-20000363219990529
     TR 200003632
                       T2
                            20010420
                                           AU 2000-53394
                                                            20000816
     AU 761249
                       B2
                            20030529
                                                            20001130
    ZA 2000007060
                                           ZA 2000-7060
                            20010718
                      Α
                                           ZA 2000-7061
                                                            20001130
                            20010718
     ZA 2000007061
                      A
                                           US 2000-719047
                                                            20001207
                           20020514
     US 6387944
                       В1
                                           US 2001-773772
                                                            20010202
                            20020418
     US 2002045583
                      A1
                            20020827
                       B2
     US 6441022
                                           DE 1998-19825804 19980610
PRIORITY APPLN. INFO.:
                                           AU 1997-23266
                                                            19970311
                                           WO 1999-EP3701
                                                            19990528
                                           US 1999-398315
                                                            19990920
GΙ
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *
    Title compds. such as I (mixture of diastereoisomers) were prepared as
AΒ
    hypolipemic agents. Thus, I was prepared in 2 sequences from racemic II and
     Fmoc-D-lys(Boc)-OH, followed by removal of the Fmoc group with Et2NH. I
     was ≥20 times more active than 3 analogous comparison substances in
     tests of fecal separation of 14C-taurocholic acid in rats.
    ICM C07D337-08
IC
         C07K005-068; A61K031-38
     ICS
     27-21 (Heterocyclic Compounds (One Hetero Atom))
CC
     Section cross-reference(s): 1
     amino acid benzothiepine dioxide deriv prepn hypolipemic
ST
IT
     Hypolipemic agents
        (amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as)
     252372-02-4P
IT
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); SPN (Synthetic preparation); BIOL (Biological
     study); PREP (Preparation)
        (amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as
hypolipemic
        agents)
                  252047-42-0
     92122-45-7
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as
hypolipemic
        agents)
                    252372-01-3P
     252372-00-2P
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (amino acid containing benzo[b]thiepine 1,1-dioxide derivs. as
hypolipemic
        agents)
                               THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS
REFERENCE COUNT:
                         1
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
L19 ANSWER 10 OF 13 MARPAT COPYRIGHT 2004 ACS on STN
                         132:22884 MARPAT
ACCESSION NUMBER:
                         Preparation of benzothiepine-1,1-dioxides as
TITLE:
```

Shears

Searcher :

571-272-2528

hypolipemics

Frick, Wendelin; Enhsen, Alfons; Glombik, Heiner; INVENTOR(S):

Heuer, Hubert

Hoechst Marion Roussel Deutschland G.m.b.H., Germany PATENT ASSIGNEE(S):

PCT Int. Appl., 30 pp. SOURCE:

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

PATENT NO.				KI		DATE			AI		CATI	ON NO	o.	DATE				
WO	9964 9964	409 409		A: A:	2	1999	0302			19	99-E	P374:		1999				
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		DE.	DK.	EE.	ES.	FI,	GB,	GD,	GE,	GH,	GM,	HR,	ΗU,	ID,	IL,	IN,	IS,	
		JP.	KE.	KG.	KP.	KR,	KZ.	LC,	LK,	LR,	LS,	LT,	LU,	LV,	MD,	MG,	MK,	
		MN.	MW.	MX.	NO.	NZ,	PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	
		TM.	TR.	TT.	UA.	ŪG,	US,	UZ,	VN,	YU,	ZA,	ZW,	AM,	AZ,	BY,	KG,	ΚZ,	
		MD.	RU.	ТJ.	TM													
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		CI.	CM.	GA.	GN,	GW,	ML,	MR,	NE,	SN,	TD,	TG						
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	1982			C		2000	0824											
	2000			T		2001			\mathbf{T}^{1}	R 20	00-2	0000	3634	11999	0528			
	2182		-	Т		2003			E	s 19	99-9	2778	4	1999	0528			
	1086			Т		2003	0331		P.	г 19	99-9	2778	4	1999	0528			
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	9945			Α		1999			Α	J 19	99-4	5031		1999	0529			
	7526			В		2002	0926											
	1086			А		2001	0328		E	P 19	99-9	2780	2	1999	0529			
	1086	113		В	1	2004												
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	IT,	LI,	LU,	NL,	SE,	PT,	ΙE,	FΙ
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JP	2002	5174	90	Т	2	2002	0618		J	P 20	00-5	5341	8	1999	0529			
JР	3374	129		В	2	2003	0204											
ΝZ	5086	81		Α		2002	0628							1999				
RU	2220	141		С	2	2003	1227		-			0149		1999				
ΑT	2593	72		E		2004	0215					2780			0529			
US	6221	897		В	1	2001	0424			. –		9831	_	1999				
AU	7612	49		В	2	2003	0529					3394		2000				
zA	2000	0070	60	A		2001	0718			A 20					1130			
zA	2000	0070	61	A		2001	0718			A 20					1130			
ИО	2000	0062	51	А		2001	0207			0 20			_		1208			
US	2002	0455	83	А	.1	2002	0418		U	S 20	01-7	7377	2	2001	0202			
បន	6441	.022		В	2	2002	0827						_					
US	2003	0179	96	A	.1	2003	0123		U	S 20	02-2	0105	0	2002	0724			
US	6642	269			2	2003							_		0.505			
US	2004	0876	48	А	.1	2004	0506					0677			0627			
ORIT	Y APE	LN.	INFO).:										1998				
												3119			0311			
												3266			0311			
												P374			0529			
									U	S 19	99-3	9831	.5	T998	0920			

US 2001-773772 20010202 US 2002-201050 20020724

GΙ

Title compds. [I; R = C6H4NHZR3; R1,R4,R5 = Me, Et, Pr, Bu; R2 = H, OH, amino(alkyl); R3 = sugar residue; Z = bond, carbonyl(alkylene), CONH, etc.] were prepared Thus, I [R = C6H4(NHR')-3, R1 = Et, R2 = OH, R4 = R5 = Me](II; R' = H) was amidated by penta-O-acetyl-D-gluconic acid and the product deprotected to give II (R' = gluconoyl) as a mixture of diastereomers. Data for biol. activity of I were given.

IC ICM C07D337-00

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

ST benzothiepine dioxide prepn hypolipemic

IT Hypolipemic agents

(benzothiepine-1, 1-dioxides)

IT 252047-36-2P 252047-37-3P 252047-38-4P 252047-39-5P 252047-40-8P 252047-41-9P 252208-66-5P 252208-67-6P 252208-68-7P 252208-69-8P 252208-70-1P 252208-71-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of benzothiepine-1,1-dioxides as hypolipemics)

IT 488-43-7, D-Glucamine 2432-99-7, 11-Aminoundecanoic acid 17430-71-6, Penta-O-acetyl-D-gluconic acid 53555-69-4 252047-42-0 252047-43-1 RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of benzothiepine-1,1-dioxides as hypolipemics)

IT 252047-44-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of benzothiepine-1,1-dioxides as hypolipemics)

L19 ANSWER 11 OF 13 MARPAT COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

131:58769 MARPAT

TITLE:

Preparation of enantiomerically-enriched

tetrahydrobenzothiepine oxides by cyclization of

arylpropanalsulfoxides.

INVENTOR(S):

Li, James; Wang, Ching-Cheng; Reitz, David B.;

Snieckus, Victor; Huang, Horng-Chih; Carpenter, Andrew

J.

PATENT ASSIGNEE(S):

SOURCE:

G.D. Searle and Co., USA PCT Int. Appl., 100 pp.

CODEN: PIXXD2

Searcher: Shears 571-272-2528

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

PATENT NO.						DATE			A)	PPLI	CATI	ON NO	0.	DATE				
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	9917	213		A	1	1999	0712		A	ປ 19	99-1	7213		1998	1216			
	1042			A	1	2000	1011		E.	b 19	98-9	6204	4	1998	1216			
EP	1042	314		В	1	2003	0319								~-			
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	IT,	LI,	LU,	NL,	SE,	PT,	IE,	F.T
JP	2001	5262	84	T	2	2001	1218		J	P 20	00-5	2541	5	1998	1216			
BR	9814	300		Α		2002	0205		B.	R 19	98-1	4300		1998	1216			
AT	2348	29		E		2003	0415		A.	I. TA	90-9	0204	4	1990	1210			
CN	1106	395		В		2003	0423		C)	N 19	98-8	1360	9	1998	1216			
	1331	225		А	1	2003	0730		E	P 20	03-5	459		1998	1216			
	R: 2195 9811	428			3	2003	1201		E	s 19	98-9	6204	4	NL, 1998 1998	1216	PT,	IE,	FI
2A.	7612	40		B		2003	0529		A1	u 20	00-5	3394		2000	0816			
AU	7612 6369	220		B		2003	0409		11	s 20	00-5	8189	7	2000	1002			
	1034	071		ν D			0109			к 20	01-1	0574	3	2001	0815			
пк	2002	1001	1.0	ν 	1	2001	1212		11	5 20	02-7	2600	•	2002	0211			
			19	Α.	T	2002	0903		۵.	N 20	02 , 03-1	0704	6	2003	0228			
	1439					2003	0903			n 20	97-6	8170		1997				
PRIORIT	Y APP	, LN.	TNFO	. :										1997				
												6204		1998				
													_	1998				
														2000				
								1 [a 20	00-5	8189	1	2000	1002			
OTHER S	OURCE	:(S):			CAS	REAC	т 13	1:28	169									

GΙ

$$R^{6}$$
 R^{7}
 R^{1}
 R^{2}
 R^{2}
 R^{3}
 R^{2}
 R^{2}
 R^{3}
 R^{2}

I

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Title compds. [I; R1, R2 = H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl,
AΒ
     heteroaryl; R3 = H, (substituted) alkyl, alkenyl, alkynyl, aryl,
     cycloalkyl, heterocyclyl, etc.; R4-R7 = H, alkyl, alkenyl, alkynyl,
     cycloalkyl, aryl, heteroaryl, halo, alkoxy, aryloxy, NO2, amino; R3 and
     the OH are syn], were prepared by cyclization of enantiomerically-enriched
     aldehydes (II; R1-R7 as above). Thus, enantiomerically-enriched II (R1, R2 = Bu; R4, R6, R7 = H; R5 = F; R3 = 4-MeOC6H4) (preparation given) was
     stirred with KOCMe3 in THF at -15° to give 77.7% (4R,5R)-I
     (variables as before).
IC
     ICM C07D337-08
         C07D487-08; C07D487-08; C07D241-00; C07D241-00
CC
     27-21 (Heterocyclic Compounds (One Hetero Atom))
     benzothiepine oxide enantiomerically enriched prepn; arylpropanalsulfoxide
ST
     enantiomerically enriched cyclization
     Cyclization
IT
        (preparation of enantiomerically-enriched tetrahydrobenzothiepine oxides
bу
        cyclization of arylpropanalsulfoxides)
     127184-05-8 139628-16-3
ΙT
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (chiral oxidant; preparation of enantiomerically-enriched
        tetrahydrobenzothiepine oxides by cyclization of
        arylpropanalsulfoxides)
     135620-04-1
IT
     RL: CAT (Catalyst use); USES (Uses)
        (chiral oxidation catalyst; preparation of enantiomerically-enriched
        tetrahydrobenzothiepine oxides by cyclization of
        arylpropanalsulfoxides)
     228113-61-9P
IT
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (enantiomerically-enriched; preparation of enantiomerically-enriched
        tetrahydrobenzothiepine oxides by cyclization of
        arylpropanalsulfoxides)
     546-68-9, Titanium tetraisopropoxide 13811-71-7, Diethyl D-tartrate
IT
     RL: CAT (Catalyst use); USES (Uses)
        (preparation of enantiomerically-enriched tetrahydrobenzothiepine oxides
bу
        cyclization of arylpropanalsulfoxides)
     228113-62-0P
ΙT
     RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic
     preparation); PREP (Preparation); RACT (Reactant or reagent)
        (preparation of enantiomerically-enriched tetrahydrobenzothiepine oxides
by
        cyclization of arylpropanalsulfoxides)
     75-91-2, tert-Butyl hydroperoxide 80-15-9, Cumyl hydroperoxide
IT
     93-59-4, Benzoyl hydroperoxide
                                      124-40-3, reactions 371-41-5,
     4-Fluorophenol 596-75-8, Diethyl dibutylmalonate 824-94-2,
                                3071-34-9, Benzyl hydroperoxide
                                                                    3240 - 34 - 4,
     4-Methoxybenzyl chloride
     Iodobenzene diacetate
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (preparation of enantiomerically-enriched tetrahydrobenzothiepine oxides
by
        cyclization of arylpropanalsulfoxides)
     1426-54-6P 3670-91-5P 24765-57-9P, 2,2-Dibutyl-1,3-propanediol
IT
                    228113-57-3P 228113-58-4P 228113-59-5P 228113-60-8P
     197378-20-4P
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Searcher : Shears 571-272-2528

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228113-65-3P
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
      (Reactant or reagent)
         (preparation of enantiomerically-enriched tetrahydrobenzothiepine oxides
bу
         cyclization of arylpropanalsulfoxides)
                                      228113-66-4P
                                                         228113-67-5P
ΙT
     228113-63-1P
                       228113-64-2P
     RL: SPN (Synthetic preparation); PREP (Preparation)
         (preparation of enantiomerically-enriched tetrahydrobenzothiepine oxides
by
         cyclization of arylpropanalsulfoxides)
                                   THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS
                            2
REFERENCE COUNT:
                                   RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
L19 ANSWER 12 OF 13 MARPAT COPYRIGHT 2004 ACS on STN
                             129:260353 MARPAT
ACCESSION NUMBER:
                             Preparation of ileal bile acid transport inhibiting
TITLE:
                            benzothiepines for combination therapy with HMG Co-A
                             reductase inhibitors.
                             Reitz, David B.; Lee, Len F.; Li, Jinglin J.; Huang,
INVENTOR(S):
                            Horng-Chih; Tremont, Samuel J.; Miller, Raymond E.;
                            Baneriee, Shyamal C.; Manning, Robert E.; Glenn, Kevin
                            C.; Keller, Bradley T.
                            G.D. Searle and Co., USA; et al.
PATENT ASSIGNEE(S):
                            PCT Int. Appl., 477 pp.
SOURCE:
                             CODEN: PIXXD2
                             Patent
DOCUMENT TYPE:
                             English
LANGUAGE:
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:
                                               APPLICATION NO. DATE
                       KIND DATE
      PATENT NO.
                                                _____
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                                               WO 1998-US3792 19980310
                         A2 19980917
     WO 9840375
                        A3 19981203
      WO 9840375
          W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
          DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, MI, MR, NE, SN, TD, TG
               GA, GN, ML, MR, NE, SN, TD, TG
                                                                    19980310
                        A1 19980929
                                                AU 1998-64408
      AU 9864408
                          B2
                                20010222
      AU 730024
                                                EP 1998-910075
                                                                    19980310
                          A2
                                20000119
      EP 971744
          R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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                                                                     19980310
                                                 NZ 1998-337830
                                20010727
      NZ 337830
                          A
                                                                     19980310
                                                 BR 1998-8013
                                20010925
      BR 9808013
                          Α
                                                 JP 1998-539594
                                                                     19980310
                                20020108
      JP 2002500628
                          T2
                                                NO 1999-4390
                                                                     19990910
                                19991104
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AU 2000-53394

US 2002-76091

US 1997-40660P 19970311

20000816

20020215

NO 9904390

US 2003171426

PRIORITY APPLN. INFO .:

US 6642268

AU 761249

Α

В2

A1

В2

20030529

20030911

20031104

US	1994-305526	19940913
US	1995-517051	19950821
បន	1996-13119P	19960311
ΑU	1997-23266	19970311
US	1997-816065	19970311
US	1997-831284	19970331
WO	1998-US3792	19980310
TIC	2000-676466	20000929

GI

$$(R^9)_{q} \xrightarrow[R6]{R^7}_{R^8} \\ R^1_{R^2} \\ R^3_{R^5} \\ R^4_{R^3} \\ I$$
MeO
S
S
Bu
Et
OH
II

Title compds. [I; q = 1-4; n = 0-2; R1, R2 = H, (substituted) alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, alkoxy, dialkylamino, etc.; R1R2C = cycloalkylidene; R3, R4 = H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocyclyl, heteroaryl, etc.; R3R4 = O, S, NOR11, etc.; R11 = H, alkyl, alkenyl, alkynyl, aryl, aralkyl, etc.; R5, R6 = H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, etc.; R7, R8 = H, alkyl; R9 = H, alkyl, alkenyl, alkenyl, acyloxy, aryl, aralkyl, halo, etc.], were prepared A composition comprising an ileal bile acid transport inhibitor and an HMG

Co-A reductase inhibitor is claimed. Thus, title compound (II) (preparation via 2-mercapto-4-methoxybenzophenone given) at 0.2% as an ileal perfusion in guinea pigs reduced HDL cholesterol from 89 mg% to 76 mg%.

IC ICM C07D337-00

CC 27-21 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1

ST benzothiepine prepn bile acid transport inhibitor; antihyperlipidemic benzothiepine HMG reductase inhibitor

IT Hypolipemic agents

(preparation of ileal bile acid transport inhibiting benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

IT Bile acids

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)

(transport inhibitors; preparation of ileal bile acid transport

inhibiting

benzothiepines for combination therapy with HMG Co-A reductase inhibitors)

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Searcher: Shears 571-272-2528

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L19 ANSWER 13 OF 13 MARPAT COPYRIGHT 2004 ACS on STN
                        127:307312 MARPAT
ACCESSION NUMBER:
                       Novel benzothiepines having activity as inhibitors of
TITLE:
                        ileal bile acid transport and taurocholate uptake
                        Reitz, David B.; Lee, Len F.; Li, Jinglin J.; Huang,
INVENTOR(S):
                        Horng-Chih; Tremont, Samuel J.; Miller, Raymond E.;
                        Banerjee, Shyamal C.
                        G.D. Searle and Co., USA; Reitz, David B.; Lee, Len
PATENT ASSIGNEE(S):
                        F.; Li, Jinglin J.; Huang, Horng-Chih; Tremont, Samuel
                        J.; Miller, Raymond E.; Banerjee, Shyamal C.
                        PCT Int. Appl., 406 pp.
SOURCE:
                        CODEN: PIXXD2
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DOCUMENT TYPE:
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Novel benzothiepines I [q = 1-4; n = 0-2; R = H, halo, (un)substituted alk(en/yn)yl, acyloxy, aryl, heterocyclyl, OH or NH2 or SH or derivs., etc.; R1, R2 = H, (un)substituted and/or heteroatom-replaced alk(en/yn)yl, cycloalkyl, aryl, alkoxy, alkylthio, dialkylamino; or CR1R2 = C3-10

Searcher : Shears

571-272-2528

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cycloalkylidene; R3, R4 = H, alk(en/yn)yl, acyloxy, aryl, heterocyclyl, OH
     or NH2 or SH or derivs.; or R3R4 = O, S, NH, NOH, NNH2, CH2 or derivs.;
    R5, R6 = H, (un) substituted alk(en/yn)yl, cycloalkyl, aryl, heterocyclyl,
    OH or SH or derivs.; R7, R8 = H, alkyl] and their derivs. and analogs are
    provided. Also provided are pharmaceutical compns. containing I and methods
    of their medical use, particularly in the prophylaxis and treatment of
    hyperlipidemic conditions, such as those associated with atherosclerosis or
    hypercholesterolemia. For instance, the keto aldehyde II was cyclized by
    Zn/TiCl3, and the resultant cycloolefin was oxidized and epoxidized by
    m-ClC6H4C(0)00H and hydrogenated over Pd/C to give epimeric title compds.
    \alpha- and \beta-III in 25% and 13% yield, plus addnl. compds. In a
    test for inhibition of IBAT-mediated uptake of [14C]-taurocholate in H14
    cells in vitro, \beta\text{-III} had an IC50 of 5 \mu M.
    ICM C07D337-08
    ICS C07D409-10; C08G065-329; A61K031-38
    27-21 (Heterocyclic Compounds (One Hetero Atom))
    Section cross-reference(s): 1
    benzothiepine prepn antihyperlipidemic antihypercholesterolemic
    antiatherosclerotic; bile acid transport inhibitor benzothiepine prepn;
    taurocholate uptake inhibitor benzothiepine prepn
    Antiarteriosclerotics
        (antiatherosclerotics; preparation of benzothiepines as
antihyperlipidemics)
     Intestine
        (ileum, inhibitors of ileal bile acid transport; preparation of
        benzothiepines as antihyperlipidemics)
    Bile acids
     RL: BPR (Biological process); BSU (Biological study, unclassified); MSC
     (Miscellaneous); BIOL (Biological study); PROC (Process)
        (inhibitors of ileal bile acid transport; preparation of benzothiepines
        antihyperlipidemics)
    Anticholesteremic agents
    Hypolipemic agents
        (preparation of benzothiepines as antihyperlipidemics)
     197378-62-4P
     RL: BYP (Byproduct); PREP (Preparation)
        (byproduct; preparation of benzothiepines as antihyperlipidemics)
     81-24-3, Taurocholic acid
     RL: BPR (Biological process); BSU (Biological study, unclassified); MSC
     (Miscellaneous); BIOL (Biological study); PROC (Process)
        (inhibitors of taurocholate uptake; preparation of benzothiepines as
        antihyperlipidemics)
                               24632-01-7P, 1-(Hydroxymethyl)cyclohexanecarboxa
                  3670-91-5P
     1515-89-5P
             25784-91-2P, 2-Chloro-5-nitrobenzoyl chloride
     ldehyde
                    120936-00-7P, O-2-Benzylphenyl dimethylthiocarbamate
     120454-34-4P
                    162632-54-4P, 2-Mercapto-4-methoxybenzophenone
     120936-01-8P
     163445-43-0P, 2-Mercapto-5-methoxybenzophenone
                                                      173736-11-3P
                                                  178678-57-4P
                                                                 178678-58-5P
                                  178678-56-3P
                    178678-55-2P
     178678-21-2P
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                                                                 178678-64-3P
                    178678-60-9P
                                   178678-61-OP
     178678-59-6P
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                     197378-54-4P
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (intermediate; preparation of benzothiepines as antihyperlipidemics)
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                                                                   178678-26-7P
IT
                    178678-23-4P
                                    178678-24-5P
     178678-22-3P
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                                    197373-49-2P
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                    197373-55-0P
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                    197375-49-8P
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT
     (Reactant or reagent); USES (Uses)
        (preparation of benzothiepines as antihyperlipidemics)
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                    178678-30-3P
                                    178678-31-4P
                                                    178678-33-6P
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     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); USES (Uses)
        (preparation of benzothiepines as antihyperlipidemics)
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     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); USES (Uses)
        (preparation of benzothiepines as antihyperlipidemics)
                                              100-47-0, Benzonitrile, reactions
     99-60-5, 2-Chloro-4-nitrobenzoic acid
IT
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100-66-3, reactions 106-41-2, 4-Bromophenol 110-91-8, Morpholine, reactions 123-75-1, Pyrrolidine, reactions 131-57-7, 2-Hydroxy-4-methoxybenzophenone 150-76-5, p-Methoxyphenol 4-Fluorobenzyl chloride 371-41-5, 4-Fluorophenol 462-06-6, Fluorobenzene 503-29-7, Azetidine 629-09-4, 1,6-Diiodohexane 693-23-2, Dodecanedioic acid 696-63-9, 4-Methoxythiophenol 705-29-3, 3-(Trifluoromethyl)benzyl chloride 824-98-6, 3-Methoxybenzyl chloride 869-24-9, 2-(Diethylamino)ethyl chloride hydrochloride 922-63-4, 2-Ethylacrolein 1120-71-4, 1,3-Propanesultone 1680-78-0, 2-Ethyl-2-(hydroxymethyl)hexanal 1801-99-6, 2-Mercaptobenzophenone 2043-61-0, Cyclohexanecarboxaldehyde 2516-96-3, 2-Chloro-5-nitrobenzoic 2646-90-4, 2,5-Difluorobenzaldehyde 4509-90-4, 5-Bromovaleroyl 4521-31-7, 2-Mercaptobenzyl alcohol 13331-27-6, chloride 3-Nitrobenzeneboronic acid 15852-73-0, 3-Bromobenzyl alcohol 24765-57-9, 2,2-Dibutyl-1,3-propanediol 28994-41-4, 2-Hydroxydiphenylmethane 33663-73-9, 2-Chloro-4-nitrobenzophenone 34052-37-4, 2-Chloro-5-nitrobenzophenone 35730-09-7, 2,5-Difluorobenzoyl chloride 36839-55-1, 1,2-Bis(2-iodoethoxy)ethane 99376-14-4 197378-59-9 197378-60-2 197378-61-3 121559-53-3 RL: RCT (Reactant); RACT (Reactant or reagent) (starting material; preparation of benzothiepines as antihyperlipidemics)

FILE 'MARPATPREV' ENTERED AT 09:34:05 ON 26 AUG 2004 STR

VAR G1=H/OH/NH/17

VAR G2=ME/ET/I-PR/N-PR/I-BU/N-BU/S-BU/T-BU

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

MLEVEL IS CLASS AT 18 19

GGCAT IS LOC AT 18

GGCAT IS UNS AT 19

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES: RING(S) ARE ISOLATED OR EMBEDDED NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE

L16

ATTRIBUTES SPECIFIED AT SEARCH-TIME: ECLEVEL IS LIM ON ALL NODES ALL RING(S) ARE ISOLATED

L20 0 SEA FILE=MARPATPREV SSS FUL L16 (MODIFIED ATTRIBUTES)

Searcher : Shears 571-272-2528

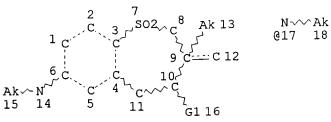
100.0% PROCESSED 0 ITERATIONS SEARCH TIME: 00.00.01

FILE 'HOME' ENTERED AT 09:34:22 ON 26 AUG 2004

0 ANSWERS

(FILE 'REGISTRY' ENTERED AT 13:29:20 ON 26 AUG 2004)

L1 STR



VAR G1=H/OH/NH/17 NODE ATTRIBUTES: DEFAULT MLEVEL IS ATOM DEFAULT ECLEVEL IS LIMITED

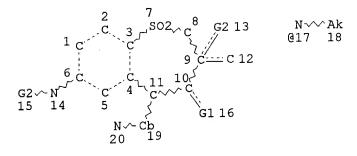
GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE

L2 649 SEA FILE=REGISTRY SSS FUL L1 L4 STR



VAR G1=H/OH/NH/17
VAR G2=ME/ME/I-PR/N-PR/I-BU/N-BU/S-BU/T-BU
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS LOC AT 18
GGCAT IS UNS AT 19
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE

L5 107 SEA FILE=REGISTRY SUB=L2 SSS FUL L4

L6 72 SEA FILE=REGISTRY ABB=ON PLU=ON L5 AND 1/NC

(FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 13:32:11 ON 26 AUG 2004) L7 0 S L6

FILE 'HOME' ENTERED AT 13:32:42 ON 26 AUG 2004

Searcher : Shears 571-272-2528